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HYPERTENSION DUE TO UNILATERAL RENAL DISEASE—WITH A REPORT ON A FUNCTIONAL TEST HELPFUL IN DIAGNOSIS

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INTRODUCTION

The classical experiments of Goldblatt (1) in 1934 demonstrated that hypertension could be produced in some dogs by the reduction in arterial blood flow to one kidney. The hypertension was eliminated by the restitution of normal renal arterial flow or by the surgical removal of the ischemic kidney. Thus experimentally a cause and effect relationship between renal ischemia and hypertension seemed clearly established.

In 1937, Butler (2) reported a patient who recovered from hypertension following nephrectomy for unilateral pyelonephritis. In the subsequent years there was a flurry of enthusiasm for the extirpation of kidneys in hypertensive individuals on almost any evidence of unilateral renal abnormality. Improvement in the hypertension resulted so infrequently that the procedure has fallen into disrepute (3). Yet there are well documented instances wherein removal of an ischemic kidney (4–8) or the reestablishment of an adequate renal blood flow (9) was followed by a disappearance of the hypertension. How then is the physician to recognize those patients who will benefit from nephrectomy? If the premise be granted that in *some* individuals reduced arterial flow to one kidney or sizable segments thereof can induce hypertension, clearly there is need for a functional test to distinguish these patients.

In search of a clue with which to indict one kidney as a cause of hypertension, the authors were impressed with Dr. Harvey White's observations in the dog (10, 11). Changes in renal function followed the gradual diminution of the caliber of one renal artery when the other was left intact. Urine from each kidney was obtained *simultaneously*, and White observed that on the ischemic side urine volume was uniformly reduced, and the sodium concentration in this sample was also lowered, often *before* either inulin or hippurate clearances were measurably altered. In one of our patients (previously re-

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ported [Ref. 8—case No. 4]) who had severe hypertension, *normal* intravenous pyelograms, and demonstrable constriction of the right main renal artery by aortogram, simultaneous ureteral catheterizations had been performed. Exactly such differences were found as White had described in his dogs, i.e., there was a lesser flow of urine from the kidney with the narrowed renal artery, and this specimen contained the lower sodium concentration when compared with the urine obtained from the opposite side. The ischemic kidney was later removed, and the patient's blood pressure has remained normal for three years.

Further study of simultaneously collected urine from the two kidneys in hypertensive patients was therefore undertaken. The results suggest that such data does indeed have value in predicting when disease in one kidney is responsible for hypertension. These observations form the basis of Part I of this report.

There is another group of patients who have hypertension associated with a non-functioning kidney (no urine excreted by this kidney). This group will be discussed separately in Part II.

PART I

Ureteral Catheterization Studies

Procedure[4]

1. *Preparation of patient:* Diets of normal sodium content were given for four or five days preceding the test because of the very low sodium concentrations found in the urine of individuals who had been on extreme salt restriction. During the hour preceding the catheterization, the patients ingested 200 cc. of water every 15 minutes to assure adequate urine flow. Water administration was continued at this rate during the procedure if urine flow seemed retarded. Pre-cystoscopic sedation with one of the barbiturate or opiate preparations was occasionally used. A general anesthetic was regularly administered to children, but was given to only a few of the adults in the "essential hypertension" group. When general anesthesia was used, intravenous fluids were given, averaging 5–10 ml. of 5 per cent glucose in water/kg. body weight, during the 30 minutes before the cystoscopy, and were continued at the rate of 0.1–0.2 ml./kg./minute throughout the procedure. In a few instances, intravenous 0.9 per cent sodium chloride was used instead of glucose in water, but the latter was preferred for reasons to be mentioned later.

2. *Urological procedure:* Xylocaine (2 per cent solution) was inserted into the urethra for local anesthesia. A cystoscope was then passed and the ureteral orifices identified. Number 6 "whistle-tip" ureteral catheters were used in most adults, smaller sizes for children. The catheters were passed up the ureters, so that the tips of the catheters rested in the pelvis of each kidney, about 2–3 cm. above the uretero-pelvic junction. The position of the catheter was checked in some instances by x-ray examination, comparing this film with the position of the kidney pelvis on a previous pyelogram. When urine flow seemed adequate (at least 1–2 ml./minute from one kidney) the cystoscope was removed and a third catheter

[4] The authors gratefully acknowledge the essential role of the urologists in the Brady Urological Institute and the Department of Gynecology of this hospital, who performed the ureteral catheterizations reported herein.

was inserted into the bladder. Each ureteral catheter was always allowed to drain for a few minutes and this urine was discarded. The bladder was then emptied completely with the aid of manual suprapubic compression. Immediately afterward, chemically clean Erhlenmeyer flasks were placed under each of the three catheters and the collections were begun. As soon as 50 ml. of urine had been obtained from one kidney (this usually required 20–40 minutes in a properly hydrated patient), the bladder was emptied again to determine how much (if any) urine leaked around the ureteral catheters, thus completing the first collection period. In many instances second or third periods of simultaneous urine collection from each kidney were secured in exactly the same manner as the first. (It is preferable to obtain more than one collection period since the reliability of the test is considerably enhanced if the findings in each period are consistent.) Differential phenolsulfonphthalein tests were carried out in some patients after the completion of the collections just described. If the patient had a history of urinary tract infection, an antibiotic was given prophylactically for a few days following completion of the cystoscopy.

3. *Studies on the urine obtained by catheterization:* Each specimen was measured in graduated cylinders, and if the sample contained blood, hematocrit determinations were carried out on the urine. The entire sample from each flask was then placed in 50 ml. centrifuge tubes and spun down for 20 minutes at 2000 RPM. Any hemolysis was noted, and the supernatant removed and saved in glass tubes for electrolyte analysis. Sodium (12) and chloride (13) concentrations were regularly determined and, when sufficient volume was available, potassium (12), calcium (14) and phosphorus (15) analyses were also performed. If hemolysis was present potassium determinations were not carried out. When the volume of the packed red cells in the urine was greater than 1.0 per cent (an infrequent occurrence), a correction was made in the results. It was assumed that an equal amount of plasma had been introduced into the sample (i.e., if the hematocrit on the urine was 1 per cent, then the specimen contained 1 per cent plasma). The amount of electrolyte in the contaminating plasma was estimated and subtracted from the value obtained on analysis of the urine. At best, this method of correcting for blood in urine was crude, but it permitted one to evaluate more accurately the significance of electrolyte differences in the samples collected, especially in those situations where the urine from one kidney was clear, and that obtained from the opposite side was bloody.

Results

Group A—Patients with "Essential" Hypertension

Thirty-one patients (Table I) were considered to have "essential" hypertension. The following criteria were met: a family history of hypertension, gradually increasing blood pressure levels, consistently greater than 150/90 (90 per cent of the patients had readings in the range of 170/110–250/130), no history of antecedent renal disease, normal intravenous pyelograms (in most cases retrograde pyelograms were carried out, and these were likewise normal), blood non-protein nitrogen less than 40 mg. per cent, phenolsulfonphthalein excretion greater than 55 per cent in two hours, ability to concentrate urine to a specific gravity of 1.020 or more and a normal urinalysis (a few patients showed a trace to 1 plus proteinuria). Most of the subjects had benzodioxane and/or regitine tests performed, but none suggested the presence of pheochromocytoma.

In this group of patients urine samples obtained simultaneously from the

TABLE I

(GROUP A)

Ureteral Catheterization Studies in Patients with Essential Hypertension

Patient No.	Urine Volume ml.			Sodium mEq./L.			Chloride mEq./L.		
	Left	Right	Bladder	Left	Right	Bladder	Left	Right	Bladder
1	20	25	0	12	10				
2	36	30	0	2	2		4	3	
3	135	110	0	134	131		121	120	
4	55	52	0	27	28		21	25	
5	56	62	0	47	46		13	12	
6	47	50	0	62	63		65	67	
7	48	48	0	6	6		5	4	
8	52	44	0	136	132		137	136	
9	56	50	0	11	12		16	17	
10	21	23	0	181	180		196	193	
11	47	45	2	142	140		132	121	
12	47	52	56	35	35	32	34	33	34
13	46	50	1	22	21		22	19	
14	59	69	4	14	15		19	20	
15	30	13	90	131	129	138	166	173	161
16	61	54	0	189	187		216	221	
17	37	34	350	18	17	17	17	16	15
18	99	24	70	6	5		8	8	
19	40	48	0	39	41		35	36	
20	51	47	0	10	9		13	13	
21	27	24	98	108	108	3	104	124	3
22	55	47	1	33	32		39	38	
23	42	48	5	10	11		8	10	
24	54	53	3	14	15		16	18	
25	45	42	10	33	34				
26	121	130	0	39	40		34	36	
27	50	61	0	23	20		25	20	
28	45	38	1	185	190		178	178	
29	48	44	0	101	107		105	99	
30	50	25	200	12	12				
31	71	65	8	28	28		25	23	

two kidneys were virtually identical in volume and electrolyte concentration. When there was significant leak of urine around one or the other catheter (this occurred in six of the thirty-one patients), volume comparisons were valueless, but *sodium concentrations* were *always* nearly equal, and any difference was less than 5 per cent.[5]

[5] In those instances where the sodium concentration in the urine from each kidney was less than 12 mEq./liter, a variation of 1 to 2 mEq. between the two sides would be considered to represent a difference of 10–15 per cent. When interpreting percentage differences in sodium concentration in the urine from two kidneys, it is probably not wise to consider such slight deviations significant at these low concentrations. It is believed that sodium variations will be more accurately reflected and therefore more significant in interpretation if the concentration of this ion from one kidney is approximately 20 mEq./liter or greater.

Measurement of other electrolytes in the urine from the two kidneys, likewise produced a striking similarity in the chloride, potassium, calcium and phosphorus concentrations. In a few instances, the percentage difference between the two sides was greater than that for sodium, but the majority were nearly identical.

Group B—Patients with Hypertension and Bilateral Renal Disease

Additional confidence in the validity of these observations was afforded by studies in patients with bilateral renal disease (Tables II, III and IV). Each patient in Table II had a history of *rapidly progressive*, severe hypertension *of recent onset*. This clinical picture was nearly identical with that seen frequently when hypertension was caused by unilateral renal vascular disease (8, 16); so it was of the greatest diagnostic and therapeutic importance to clearly distinguish this group. At the time the ureteral catheterizations were performed on these patients, the nature of the underlying disease process was not known.

Analysis of the data in Table II reveals that urine volume was not always identical from the two kidneys (being reduced 50 per cent on one side in two instances) but *sodium concentration* in the urine was the *same* or slightly *greater* on the side with the *lesser* urine volume. On the basis of these findings, it was thought that disease in one kidney was not responsible for the hypertension, and if the elevated blood pressure were of renal origin, bilateral disease must

TABLE II

Patients with Severe Hypertension and Bilateral Renal Disease

(Hypertension of *abrupt onset*, less than 3 months duration, diastolic B.P. > 110)

Patient	I. V. pyelogram	N. P. N. mg. %	Urine				Pathologic Diagnosis
			Volume in ml.		Sodium mEq./L.		
			Left	Right	Left	Right	
T.D.J.* WM 55	Normal	25–26	21	27	22.5	23.4	Died 6 weeks after test. Autopsy: periarteritis nodosa involving kidneys only.
H.P. WM 26	Normal	33–34	17	7	24.2	24.2	Died 1 year after test, in uremia. Autopsy: chronic intercapillary glomerulonephritis.
W.S.* WM 24	Slightly delayed excretion bilateral	39–46	27	51	197.0	113.0	Negative exploration for pheochromocytoma. Biopsy of both kidneys: arteriolosclerotic nephritis with glomerular crescents and tubular hemorrhages. (malignant hypertention).

* Abdominal aortograms revealed a normal renal vascular pattern.

TABLE III

(GROUP B)

Ureteral Catherization Studies in Patients with Hypertension and Bilateral Renal Disease

Patients	Urine Volume ml.			Sodium mEq./L.			Chloride mEq./L.			Evidence for Bilat. Disease
	Left	Right	Bladder	Left	Right	Bladder	Left	Right	Bladder	
A. L.	23	40	33	35	35		24	41		Bilateral hydronephrosis, NPN 100 mg.%
G.L.	62	16	3	14	32		23	34		NPN 70 mg.%, PSP 20% in 2 hr.
O.D.	50	50	0	58	45		58	42		Acute glomerulonephritis
F.G.	45	36	0	79	83		97	100		PSP 30% in 2 hr.
W.H.	30	30	32	9	9	12	20	20	24	Repeated urinary tract infections, bilateral deformed calyces by pyelogram
F.R.	35	44	138	33	37	9	50	53	9	Malignant hypertension, NPN 52 mg.% PSP 14% in 2 hr.
B.C.	48	61	?	53	55		63	62		Bilateral polycystic disease (confirmed at operation)
M.R.	27	49	12	60	63	63	63	62	67	PSP 40% in 2 hr.
A.S.	22	34	0	31	26		27	23		NPN 44 mg.%
H.F.	38	39	7	58	61	62	50	50	49	NPN 71 mg.%
M.J.	48	48	0	40	39		39	39		NPN 54 mg.%

TABLE IV

(GROUP B)

Bilateral Extrinsic Ureteral Obstruction with Moderate Hydronephrosis

I. V. Pyelogram—good excretion on right; only faint concentration of dye on left
D.F.. Age 48 B.P. 190/110 NPN 45–55 mg. %

Date 1955	Time in minutes	Volume* ml.		Sodium mEq./L.	
		Left	Right	Left	Right
July 14	60	14	29	42	24
July 15	55	25	48	43	19
July 16	30	30	62	28	12
July 18	40	34	50	41	20
July 19	55	30	53	71	48

* No leakage observed around ureteral catheters during collection periods.

be present. The subsequent course of these patients provided histologic evidence which proved these suppositions to be correct.

In Table III is listed the data from eleven hypertensive patients considered to have bilateral renal disease because of the presence of azotemia (N.P.N. > 40 mg. per cent), impaired phenolsulfonphthalein excretion (less than 45 per cent excretion of the dye in two hours), or definite pyelographic evidence of disease in both kidneys. No histological evidence was available to determine

the exact nature of the renal disease. The ureteral catheterization data obtained in these subjects was very similar to that of the patients with proven bilateral renal disease (Table II). Some differences in urine volume between the two sides were noted, but urine sodium concentrations were nearly identical or even *higher* on the side that put out the *lesser* volume. The chloride concentrations were less consistent. Other electrolyte determinations were carried out on only two of these patients, so that these data are not included.

Another example of the consistency of the catheterization studies was provided by a series of observations on a patient with hypertension, mild azotemia, and bilateral ureteral obstruction and hydronephrosis, in whom the ureteral catheters were passed beyond the site of obstruction into the kidney pelves and kept in place for six days (Table IV). During this time, simultaneous collections of urine were made from the catheters for brief periods each day. The results indicated that there was a difference in urine volume and sodium concentration between the two sides (similar to the pattern in Tables II and III), but these differences remained strikingly *consistent* during the entire time the catheters were in place.

Group C—Patients in Whom Nephrectomy Alleviated Hypertension

Four patients with severe hypertension have been observed in whom ureteral catheterization studies have shown the same pattern that White (10) (11) found in his dogs when he produced unilateral renal artery constriction, viz., the urine from one kidney showed a significant *reduction* in both volume and sodium concentration as compared with urine obtained *simultaneously* from the opposite side (Table V). Two of these patients (I.N. and R.M.) had arteriographic evidence of impaired blood supply to the kidney that was excreting the lesser urine volume with the lower sodium concentration. The other two individuals did not have aortograms performed. By coincidence, the right kidney was the diseased side in each subject. Note that patient N.T. had the test performed three times with consistent differences during each study period.[6] Urine chloride determinations were performed in three of these patients, and in each instance the concentration was reduced on the right side,

[6] In patient N.T., note that the sodium concentration on the right side was 44 to 11 per cent less than that obtained from the left on repeated tests. No explanation is apparent for this variation in sodium concentration, but the significant point is that it was *always reduced* 11 per cent or more on this same side. During the third test, when the least differences in sodium concentrations were noted, the patient was given intravenous isotonic sodium chloride, resulting in much higher sodium concentrations in the urine. White and his associates noted that when their animals with unilateral renal artery constriction were loaded with salt (11), the *differences* in sodium concentration in the urine excreted by the two kidneys were less striking than when hydration with water alone was used. At the present time it is believed that intravenous sodium chloride solutions should not be given to patients during the ureteral catheterization study, and if parenteral hydration is necessary, it is preferable to use 5 per cent glucose in water.

the degree of reduction paralleling the decrease in sodium. Other electrolyte determinations were not done because of insufficient urine volume.[7]

The clinical picture in this group (Table V) was indistinguishable from that seen in patients with severe "essential" hypertension. One patient (I.N.) had a normal intravenous pyelogram. In the other three patients radiologic studies revealed the right kidney was 1.5 to 3.0 cm. smaller than the left. The catheterization data suggested that in all four subjects the right kidney was ischemic. In each case right nephrectomy was performed and marked alleviation of hypertension ensued.

The four patients have been observed for periods of ten months to three years following nephrectomy, and in each instance, blood pressure readings, symptoms and fundoscopic findings have indicated distinct improvement. One of the patients (S.B.) maintained blood pressure levels of 170/90–200/100 (without anti-hypertensive medication) during the 15 months after nephrectomy; but this represented striking benefit when compared with his preoperative status. The patient had had mild essential hypertension for 20 years (blood pressure averaging 160/90–170/100). Two years before nephrectomy there had been an abrupt rise in blood pressure with readings of 200/130–270/150 being recorded consistently. After a review of the clinical information and ureteral catheterization studies it was believed that the patient had suffered a renal vascular insult on the right side and nephrectomy was advised, with the reservation that the blood pressure should return to the previous mildly elevated levels, but not to a normotensive range. The postoperative course proved this assumption to be correct. Unfortunately, this patient had considerable vascular disease before operation as indicated by the thrombosed central retinal artery and the finding of advanced arteriosclerosis in the excised kidney. The vascular disease ultimately resulted in a cerebral catastrophe and death of the individual 15 months after nephrectomy.

TABLE V
(GROUP C)
Patients in Whom Nephrectomy Alleviated Hypertension

Group D—Patients in Whom Nephrectomy Had No Beneficial Effect on Hypertension

The clinical and ureteral catheterization data on these four patients is listed in Table VI. Each presented with hypertension and an abnormality in one kidney demonstrated by intravenous pyelograms. A diminution in kidney size, with or without changes of pyelonephritis, with smaller renal artery by arteriography (*a change which seems inevitable with atrophy from any cause*) were the radiologic indications of unilateral renal disease in three patients. The other subject (V.H.) was thought to have a tumor in the left kidney.

[7] Differential phenolsulfonphthalein determinations were also carried out. With each test there was a reduction in dye excretion from the diseased side, this kidney excreting from 40 to 90 per cent less dye than its companion in a given time period. But, as will be noted from the studies in Group D, this differential dye test is not considered a reliable guide in determining when disease in one kidney is causing hypertension.

TABLE V
(GROUP C)

Patients in Whom Nephrectomy Alleviated Hypertension

Patient, History No.	Age, Race, Sex	Blood Pressure (mm. Hg)	Duration of Hypertension before Nephrectomy	Optic Fundi	X-Rays		Laboratory Data				Ureteral Catherization Results						Operation and Follow up	Pathologic Findings in Excised Kidney
					Pyelogram	Aortogram	Blood NPN (mg.%)	Urine			Vol.* ml.		Sodium mEq./L.		Chloride mEq./L.			
								Max. sp. gr.	Protein	PSP	left	right	left	right	left	right		
I.N.† 629194	37 W M	200–240 / 110 140	2–6 months	Retinal arteriosclerosis, moderate a-v compression, hemorrhages and exudates	*Normal:* intravenous and retrograde study	localized constriction of rt. renal artery near its origin from aorta	32	1.020	0–1+	32% ½ hour	100	10	19	12	—	—	Nephrectomy, right 1/28/53. *Follow-up*—38 months; B.P. constantly 140/80–150/95. Fundi normal by 9th month.	Normal kidney except for some hypertrophy of juxtaglomerular apparatus
R.M. 647838	50 W M	160–220 / 100 120	Mild B.P. elevation 4 years; 220/120 for 6 months.	Blurring of disc margins with marked narrowing of arteries	*Retrograde:* normal except right kidney 1.5 cm. shorter than left	No main renal artery on right. Lower one-half of right kidney contained no dye	35	1.022	0–1+	47% 2 hours	22	9	117	99	140	112	Nephrectomy, right 9/18/53. *Follow-up*—34 months; B.P. consistently 140/75–160/90. Fundi normal by 10th month.	Weight—112 gm. Many intrarenal arteries occluded with cholesterol emboli; widespread "ischemic" tubular atrophy§
S.B. 696425	61 W M	220–270 / 130 150	Mild hypertension 160–170/100 for 20 years; B.P. > 220/120 for 2 years	Occlusion of central retinal artery, left. Severe arteriosclerosis and hemorrhages in right	*Intravenous:* Normal except right kidney smaller; *left:* 11.5 cm.; *right:* 8.5 cm.	not done	35	1.015	trace	75% 2 hours	53	5	19	13	19	14	Nephrectomy, right, 2/21/55. *Follow-up*—15 months; B.P. consistently 170/90–200/100; developed cerebral thrombosis in 11th month. Died 15 months post-op. of another cerebral vascular accident. No autopsy.	Weight—65 gm. Cortex narrowed. Severe intrarenal arteriosclerosis. Cholesterol emboli in medium sized arteries. Focal areas of "ischemic" tubular atrophy§
N.T.‡	20 W F	180–240 / 110 140	2 years. (No history of urinary tract infection)	Moderate narrowing of arteries	*Intravenous:* normal except right kidney smaller; *left:* 12.5 cm.; *right:* 10.0 cm.	not done	38	1.020	trace (urine culture sterile)	67% 2 hours	50 50 61	13 4 8	48 43 119	40 24 106	Dec. 1. '55 Dec. 5. '55 Jan. 31. '56		Nephrectomy, right 2/3/56. *Follow-up*—10 months; B.P. consistently 120/70–130/80. Fundi—normal.	Chronic pyelonephritis; widespread "ischemic" tubular atrophy§

* No leakage of urine occurred around the ureteral catheter during these studies.

† This patient previously reported (8).

‡ Seen through courtesy Drs. Jos. Menning and Lester Lebo at South Baltimore General Hospital. Baltimore, Maryland.

§ "Ischemic" tubular atrophy is discussed in Part III.

TABLE VI

(GROUP D)

Patients in Whom Nephrectomy Had no Beneficial Effect on Hypertension

Patient History No.	Age, Race, Sex	*Blood Pressure (mm. Hg).	Duration of Hypertension before Nephrectomy	Optic Fundi	X-Rays		Laboratory Data				Ureteral Catherization Results									Operation and Follow-up	Pathologic Findings in Excised Kidney
					Pyelogram (Intravenous and Retrograde)	Aortogram	Blood NPN (mg.%)	Urine			Date	Volume ml.			Sodium mEq./L.			Chloride mEq./L.				
								Max. sp. gr.	Protein	PSP		†L.	R.	B.	†L.	R.	B.	†L.	R.	B.		
V.H. 659558	57 W M	190–240 / 105 145	7 years	Blurring of both nerve heads. Narrowed arteries, hemorrhages	Normal except for mass arising from upper pole left kidney displacing it laterally; upper calyces on left poorly filled with dye	not done	43	1.010	2+	47% 2 hours	Dec. 1953	35	55	0	5	4	—	—	—	—	Nephrectomy, left 12/21/53. *Follow-up*—11 months; B.P. 195/110 at rest. NPN. 44 mg%	Cyst filled with blood in upper pole. Cortex of upper ⅔ of kidney narrowed. Lower ⅓ of kidney supplied by aberrant artery. *Micro.* — marked intrarenal arteriosclerosis. Few areas "ischemic" tubular atrophy
P.W. 635780	18 W F	140–165 / 90 110	2 years	Arteries slightly narrowed and tortuous	Normal except left kidney smaller; *left:* 7 cm.; *right:* 15.5 cm. Calyces on left blunted and contracted	Small main renal artery on left; no evidence impaired arterial flow to left kidney	29	1.018	0 (urine culture sterile)	60% 2 hours	Sept. 1954	6	47	10	24	21	25	26	22	29	Nephrectomy, left 5/20/55 *Follow-up*—17 months; B.P. 150/95–165/105	Weight — 23 gm. Cortex scarred, and dilated pelvis. *Micro.* — chronic pyelonephritis. No "ischemic" tubular atrophy
											May 1955	12	23	104	16	17	16	13	14	13		
B.H. 706909	42 C F	165–180 / 105 130	8 years	Slight narrowing of arteries	Right kidney small—about ½ size of normal left kidney. Calyces blunted on right	not done	27	1.020	0–1+	65% 2 hours	June 1955: Per. I	38	6	0	19	26	—	24	25	—	Nephrectomy, right, 6/15/55. *Follow-up* — 12 months B.P. 170/115–150/105	Small & contracted. Distorted corticomedullary outlines. *Micro* — Same as P.W. (above) (Fig. 6)
											Per. II	12	2	44	28	36	23	31	34	27		

TABLE VI—*Continued*

						blunted on right																						

TABLE VI—*Continued*

L.B. B27977	9 W F	150–180 / 110 130	2 months; (B.P. normal at time of bilaterial nephrolithotomy for cystine stones 20 months before)	Minimal narrowing of arteries	Left kidney normal. Right kidney 2 cm. smaller than left. Calyces on right dilated and blunted	Main right renal artery smaller than left; no evidence of impaired renal circulation	33	1.024	0–trace	95% 2 hours	Mar. 1956 (a):‡										Nephrectomy, right, 3/26/56. *Follow-up*—6 months B.P. 150/110–170/130	Kidney shrunken. Distorted cortical and medullary outlines; pelvis dilated. *Micro.*—same as P. W. (above)
											Per. I	45	18	36	20	22	13	16	19	9		
											Per. II	28	15	61	14	16	10	11	16	9		
											Mar. 1956 (b):‡											
											Per. I	45	3	11	41	40	42	52	46	70		
											Per. II	35	4	26	41	41	41	47	56	46		

* All patients in Table VI had negative benzodioxane and/or regitine tests. Patient L.B. also had normal urine catechol amine excretion.

† L = left ureter; R = right ureter; B = bladder.

‡ Three week interval between studies (a) and (b).

Ureteral catheterizations showed a smaller urine volume from the "damaged" kidney, but the sodium concentration in this lesser urine was *equal to* or *greater than* that which came from the normal or more normal side. In patient L.B., leakage around one or both ureteral catheters prevented any comparison of urine volumes from the two sides. However, the sodium concentration in the urine from the small kidney was always the same or greater than that found coming from the opposite side. The concentrations of chloride, potassium, calcium and phosphorus in the urine from the two kidneys, were likewise equal or greater on the side that was excreting the smaller volume.[8]

On the basis of the urine volume and sodium results, it was predicted that the "diseased" kidney was *not* responsible for hypertension in these individuals, and therefore, nephrectomy would have no beneficial effect. Two of the patients (V.H. and B.H.) had surgical indications for removal of the diseased kidney. In the others (P.W. and L.B.), both young girls, no cause was found for the elevated blood pressure, and it was "hoped" that removal of the small kidney might alleviate the hypertension. Nephrectomy was carried out in each instance. In two of the subjects (B.H. and P.W.) there was a transient fall in blood pressure to a normotensive range, which lasted for one week following operation. In each patient, now followed for postoperative periods of six to sixteen months, nephrectomy has had no sustained beneficial effect on the hypertension.

Group E—Patients with Hypertension and Unilateral Renal Disease in Whom Nephrectomy Was Not Performed

The fifteen patients in this group (Table VII) are similar to those in Group D, in that they had hypertension and pyelographic indications of disease in one kidney. Many of the individuals also had histories compatible with previous upper urinary tract infection. The radiologic evidence included dilated, blunted and/or contracted calyces on one side and in most instances this kidney was also 1 to 5 cm. smaller than the opposite "normal" side. Bilateral simultaneous catheter studies revealed a reduction in urine volume from the "diseased" kidney, but the sodium concentration in this smaller volume of urine was equal to or greater than in that from the opposite side.

It would have been of great interest to note the effect of nephrectomy on the course of hypertension in this group. But the results of the catheterization studies were identical with the findings observed in the patients in Group D in whom nephrectomy had essentially no effect on the hypertension. Therefore operation was not carried out.

[8] Only one patient (P.W.) had a differential phenolsulfonphthalein test performed, and this indicated marked impairment of function in the abnormal kidney.

TABLE VII

(GROUP E)

Ureteral Catheterization Studies in Patients with Hypertension and Radiologic Evidence of Unilateral Renal Disease

Patient	Urine Volume ml.			Sodium mEq./L.			Chloride mEq./L.			Abnormal kidney by pyelogram
	Left	Right	Bladder	Left	Right	Bladder	Left	Right	Bladder	
L.S.	47	44	0	45	45		44	44		Right
D.S.	12	24	0	100	106		128	124		Left
V.L.	49	54	4	109	86		106	81		Right
C.W.	12	56	1	6	5		9	7		Left
E.J.	49	24	0	50	46		56	47		Right
W.C.	34	49	8	77	79	97	79	86		Right
L.S.	46	32	0	183	184		160	159		Left
E.M.	32	39	18	209	190	193	184	173	160	Right
M.T.	60	39	10	17	24		14	15		Right
D.B.	25	50	0	84	76		73	54		Left
F.B.	40	58	0	31	32		26	25		Left
A.H.	73	41	0	59	58		48	48		Right
A.W.	53	88	23	72	72	90	82	79	99	Left
H.B.	41	89	0	5	5		14	10		Left
L.L.*	Upper 34 Lower 8	102	0	Upper 49 Lower 61	47		Upper 37 Lower 53	41		Left, lower

* Patient L.L. had reduplication of left urinary tract. The left lower kidney was the smallest, measuring only one-half the size of the normal right kidney.

Group F—Patients with Unilateral Renal Disease and Normotension

There were three patients in this group (Table VIII) and two of them (L.K. and H.H.) had clinical histories and intravenous pyelograms compatible with the diagnosis of unilateral pyelonephritis. The diseased kidney was also approximately one-half the size of the opposite normal kidney by x-ray examination.

During the ureteral catheterization studies, leakage around the catheters prevented accurate volume comparisons from the two sides, but urine sodium concentrations were equal in subject H.H., and reduced slightly on the diseased side in patient L.K.

Thus, except for the absence of hypertension, the clinical, radiologic, and catheterization findings in these patients were very similar to those in Group D. Because of recurrent episodes of infection, the diseased kidney was surgically removed from patient H.H.

The third patient (P.S.) in Table VIII showed somewhat different but very instructive findings on the bilateral catheter study. This individual had *uni-*

TABLE VIII

(GROUP F)

Ureteral Catherization Studies in Patients with Normal Blood Pressure and Radiologic Evidence of Unilateral Renal Disease

Patient	Urine Volume ml.			Sodium mEq./L.			Chloride mEq./L.			Abnormal kidney by pyelogram
	Left	Right	Bladder	Left	Right	Bladder	Left	Right	Bladder	
H.H.	15	47	63	8	7	8				left
L.K.	3	48	28	17	21	19	34	37	25	left
P.S.	86	58	0	61	70		46	54		left

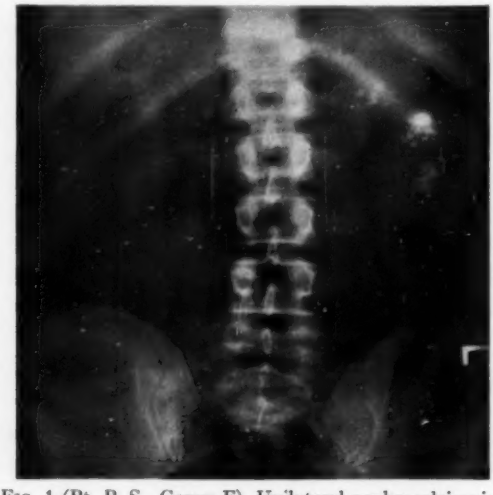

FIG. 1 (Pt. P. S., Group F). Unilateral nephrocalcinosis.

lateral nephrocalcinosis (Fig. 1) for 15 years, asymptomatic and by radiologic examination unchanged for 10 years. There was no history to suggest unilateral pyelonephritis, pyuria was absent, and urine cultures were sterile at the time of these studies. The patient's blood pressure was normal. Urine obtained coincidently from the two sides showed the *greater* volume from the calcinotic side with a slightly *lesser* concentration of sodium, chloride, potassium, calcium and phosphorus in this urine, making the *total* output of electrolytes from the calcinotic side actually greater than from the unaffected kidney. This would be interpreted as a *negative test* if hypertension had been present, since the urine volume was *greater* on the side that had the lower sodium concentration. Our premise has been that reduced arterial flow to still viable renal parenchymal tissue is reflected by *less* urine with a *lower* sodium concentration than that coming simultaneously from the opposite side (Group C—Table V).

PRECAUTIONS TO BE OBSERVED IN THE PERFORMANCE AND INTERPRETATION OF SIMULTANEOUS BILATERAL URETERAL CATHETERIZATION STUDIES

Lest the test fall into disrepute for unjustified reasons, a plea is made for care in its performance. Below are listed some of the difficulties which have been encountered.

1. A member of the medical team should be on hand to aid the urologist in carrying out the procedure. Great care must be taken in properly labelling the ureteral catheters the moment they are introduced, as well as marking the *chemically clean vessels* in which the urine is collected. The urologist has his hands full at the time and the collection and labelling should not be left to an orderly.

2. It has occasionally happened that, during a test, urine flow from one side may suddenly cease, perhaps for five to 15 minutes, and then resume. If this temporary cessation of flow went unnoticed, such a study would give spurious results. Therefore *constant* observation of the drainage from the two catheters is required. When cessation of flow occurs from one ureteral catheter, it is wise to discard the samples from both kidneys, for a major principle and virtue of the test is the comparison of urine coming *simultaneously* from the two sides.

It follows also that if urine flow is adequate, two or more collection periods of 15 to 20 minutes each are better than a single period of 30 to 45 minutes, for if the relative findings for each period remain uniform, confidence in the observations is considerably enhanced.

3. Bladder urine, which may have resulted from the escape of urine around the ureteral catheters, must always be removed at the beginning and end of a collection period, and this measured and analyzed. If there is a significant amount of leakage around the catheters, comparison of urine volumes from the two kidneys will be valueless. Occasionally, however, measuring the sodium concentration in the bladder urine will serve to identify the ureter from which the leakage occurred, but such identification should be *very cautiously* interpreted.

If the sodium concentrations in the urine from the two sides are equal, leakage around the ureteral catheters poses no problem in the final interpretation. However, if there is a significant lowering of sodium concentration from one kidney, and one cannot be certain of volume measurements because of leakage around one or both catheters, then such a test should be discarded and repeated at a later date.

The importance of accurate urine volume determinations in interpreting a ureteral catheterization study is illustrated by patient P.S. in Group F (Table VIII). The results show that one kidney was excreting urine containing a lower sodium concentration but a greater volume than the opposite side. As previously noted, such results would be interpreted as a "negative" test. If leakage of urine had occurred around the ureteral catheters, making volume comparisons impossible, the lowered sodium concentration alone on one side would have made one wonder if this were a positive test.

The results recorded in Table IV emphasize the same point. The studies indicate a consistently "negative" test. If leakage had occurred around the catheters, it would have been impossible to interpret this study. Thus accurate volume measurements, as well as sodium determinations, are *equally* important in correctly evaluating the results.

4. Much more blood in one urine specimen than the other must be given consideration. The hematocrit on such samples is determined and the plasma content estimated in order to correct for the electrolyte introduced into the specimen from the plasma. This is particularly important when only 5 to 10 ml. of bloody urine is obtained from one kidney. If the sodium concentration in this sample is 10–15 mEq./liter, a small amount of blood (hematocrit 1–2 per cent) could introduce considerable error. Thus *small* samples of *bloody* urine

with *low* sodium concentration should always be warily interpreted. If the results are doubtful after the proper corrections are made, it is suggested that the test be repeated several days later, hoping for a less traumatic catheterization, though frequently even with the most careful technique, bloody urine cannot be avoided.

5. Sometimes a catheter is inserted into one ureter and no urine appears; examination of the bladder reveals no urine present. The catheter may be occluded, and irrigation with 1–2 cc. distilled water is necessary to determine this. If the irrigation is followed by a free flow of urine, allow the catheters to drain for another 5 to 10 minutes before beginning the collections.

6. The first few ml. of urine coming from the catheters should not be included in a test period. This is especially true when hydronephrosis is present, wherein the urine that has accumulated behind an obstruction may not necessarily reflect the true functional state of the kidney (particularly as regards electrolyte concentrations). Therefore, when the test is performed on patients with hydronephrosis, the catheters should be passed beyond the point of obstruction and allowed to drain for 15 to 30 minutes before actual collections are begun. Even then, the results should be interpreted with caution, since variations in renal function may occur following relief of the obstruction. How quickly and to what degree these changes may take place would be difficult to determine in a given patient. Observations on one patient (Table IV) with bilateral hydronephrosis indicated quite consistent differences between the two kidneys from one hour to six days after the relief of the obstruction by catheters. If the urologist is unable to get the ureteral catheter beyond the obstruction, the results should be disregarded.

7. One should not attempt to interpret any test in which only 1 to 2 ml. of urine is obtained from one kidney—errors incident to such evaluation are far too great for diagnostic security.

8. Care must be exercised in cleaning the catheters. Though they may be washed with soap after usage, they should then be thoroughly cleansed with *distilled water several times.* The catheters should not be stored in solutions containing sodium, lest some contaminating electrolyte remain within and lead to inaccurate results.

9. A reasonable but not excessive state of hydration should be maintained during the collection periods. Oral hydration is preferred, as previously outlined, allowing for a urine flow of 1 to 3 ml. per minute from one kidney.

10. Finally, in evaluating the significance of the sodium concentrations in the urine, it is probably unwise to try to interpret a test when the readings are less than 10 mEq. per liter from *both* kidneys. Differences of 3 to 5 mEq. per liter between the two sides may be quite significant at this low value, but there is less likelihood for false interpretation, if the urine sodium concentration from one kidney is in a higher range.

PART II

Observations of the Course of Hypertension Following the Removal of a Non-Functioning Kidney

Within the past five years, ten patients with rather severe hypertension have been observed in whom a non-functioning kidney was discovered during the course of a diagnostic study. There are no criteria known to us whereby one may prognosticate benefit from nephrectomy in such patients. In each instance nephrectomy was performed solely on the grounds that: (1) a functionless kidney was of no value to the patient, (2) the loss of function *might*

have resulted from reduced arterial blood flow and therefore was responsible for the hypertension, (3) the only hazard to the patient appeared to be the surgical risk associated with any nephrectomy. Following operation, marked alleviation of the hypertension ensued in eight of the 10 patients. The incidence of improvement was much greater than had been expected. A review of the clinical, radiologic and laboratory features presented by the group is therefore recorded. The data have been summarized in Table IX.

The kidney was considered functionless when no dye or only the faintest trace was visualized on that side during intravenous pyelographic study (usually repeated) and the finding of no urine (or less than 1.0 ml.) from this same kidney during the bilateral catheter examination, while excellent flow (greater than 60 ml.) of urine came simultaneously from the opposite side. The opposite kidney always appeared normal in the pyelograms and in some instances was larger than average indicating probable hypertrophy.

When one kidney fails to be visualized by intravenous pyelography, one should always be wary of a congenitally absent kidney (17). One such patient was recently seen in whom only one ureteral orifice was found when catheterization study was attempted. An aortogram performed in this individual disclosed no kidney outline on one side nor any semblance of a renal arterial system on this same side.

Patients' history: All of the patients had serious symptoms from the hypertension, and the disease was classified as severe in every case. The most significant single feature in the history was the *abruptness* of the onset and relatively *brief* duration of a rapidly progressing severe hypertensive state in seven of the individuals. In four instances the hypertension had existed less than six months, and three of these patients (Nos. 6, 7, 8) were over 60 years of age. In three others, (Nos. 1, 2, 9) mild hypertension was known to have existed for several years, but in each case there had been an *abrupt increase* in the severity of hypertension within a few weeks to eight months before admission to the hospital. In the three remaining patients, moderately severe hypertension had been present for two to six years.

Only one patient in this group (No. 9) had experienced flank pain which might have signified the occurrence of a renal vascular insult. This pain had been present steadily for eight months, coinciding in onset with the severe hypertensive state.

Blood pressure: For the most part, blood pressure readings in the group ranged between 170/110–250/140, with resting levels of 160/90–180/100 being recorded in two patients.

Radiologic studies: The presence of a non-functioning kidney in each of these patients has been described. In all except three instances (Nos. 2, 4, 9, where the kidneys seemed equal in size), the functionless kidney was 1 to 5 cm. smaller than the opposite side. Retrograde pyelograms were carried out

TABLE IX

Patients with Hypertension and a Non-functioning Kidney

Patient No.	Age, Race, Sex	Blood Pressure	Duration of Hypertension before Nephrectomy	Optic Fundi	Pyelogram intravenous* and retrograde	Laboratory Data				Operation	Follow Up					Pathologic Findings in Excised Kidney
						Blood NPN mg.%	Urine				Duration in months	B.P.	NPN mg.%	PSP excretion 2 hours	Optic Fundi	
							Max. sp. gr.‡	Protein	PSP excretion 2 hours							
1.† M.P.	39 W M	140–200 / 110 130	B.P.—150/100–160/110 for 14 years; severe hypertension for 6–12 weeks.	Mild arterial narrowing and increased light reflex	*I.V.* No dye excreted by left kidney. *Ret.* normal bilaterally. *Size§: Left:* 11.5 cm.; *Right:* 15 cm.	37	1.022	0	62%	Nephrectomy, left, 1/4/52	54	140 / 95–100	—	—	Increased light reflex, otherwise normal	*Weight*—140 gm. *Gross:* Normal kidney. *Micro:* Diffuse ischemic tubular atrophy; no intrarenal vascular disease.
2.† E.G.	54 W F	170–300 / 100 150	B.P.—160–200/95 for several years; severe hypertension for 8 weeks.	Blurred left disc; severe arterial narrowing; hemorrhages and exudates.	*I.V.* No dye excreted by right kidney. *Ret.* normal bilaterally.	41–60	—	1+	50%	Nephrectomy, right, 7/15/53	24	170–200 / 80–100	44	55%	Only mod. sclerosis of arteries	*Weight*—110 gm. *Micro:* Moderate intrarenal arteriosclerosis. Cholesterol emboli in medium-sized arteries; many areas ischemic tubular atrophy.
											36	240 / 120–130	70–80	—	Same as before nephrectomy	
3. C.B.	37 W F	180–200 / 120 130	2–3 years	Narrowing and tortuosity of arteries.	*I.V.* No dye excreted by right kidney. *Ret.* collecting system distorted on right. *Size: Left:* 14 cm.; *Right:* 9 cm.	35	1.014	trace	70%	Nephrectomy, right, 8/7/53	31	110–120 / 80 90	—	—	—	*Weight*—30 gm. *Gross:* Distorted corticomedullary outlines. *Micro:* Chr. pyelonephritis with many areas ischemic tubular atrophy.
4. C.A.	43 W M	150–180 / 90 110	2 weeks; B.P. normal at time of right nephrolithotomy 16 weeks previously.	Normal	*I.V.* No dye excreted by right kidney. *Ret.* complete obstruction at ureteropelvic junction on right.	37	1.020	0	60%	Nephrectomy, right, 8/17/53	5	165 / 105	—	—	Normal	*Weight*—250 gm. *Gross:* Capsule scarred; multiple abscesses. Moderate hydronephrosis. *Micro:* Acute pyelonephritis and hydronephrosis. No ischemic tubular atrophy.
											34	150–170 / 105 110	—	—	Normal	

TABLE IX—*Continued*

5. I.K.	65 W	200–270 / 100 140	B.P.—170/90–190/100 for 18	Narrowed arteries with a-v com-	*I.V.* normal except faint dye excretion	41	1.015	trace to 1+	50%	Nephrec-	13	180 / 110	—	—	—	*Size*—9.5 x 4.5 x 3 cm. *Gross:* Thinned cortex; medulla normal; marked

TABLE IX—*Continued*

5. I.K.	65 W F	200–270 / 100 140	B.P.—170/90–190/100 for 18 years. B.P. 220/110–230/150 for six years.	Narrowed arteries with a-v compression and hemorrhages.	*I.V.* normal except faint dye excretion on right. *Ret.* normal bilaterally. *Size: Left:* 12 cm.; *Right:* 10.5 cm.	41	1.015	trace to 1+	50%	Nephrectomy, right, 4/3/54	13	180 / 110	—	—	—	*Size*—9.5 x 4.5 x 3 cm. *Gross:* Thinned cortex; medulla normal; marked narrowing of main renal artery by sclerotic plaque. *Micro:* Widespread ischemic tubular atrophy. Moderate intrarenal arteriosclerosis.
											20	220 / 150	35	—	Same as before nephrectomy	
6. R.E.	68 W M	190–200 / 90 120	2–6 months	Marked sclerosis and narrowing of arteries with a-v compression; hemorrhages and exudates.	*I.V.* right kidney small and contains 5 mm. stone; only faint conc. of dye after 45 minutes. *Size: Left:* 14 cm.; *Right:* 8 cm.	37–61	1.016	2+	24%	Nephrectomy, right, 8/6/54	18	160 / 90	50–70	—	Marked arteriosclerosis; otherwise normal.	*Weight*—60 gm. *Gross:* Scarred surface; thinned cortex; moderate hydronephrosis. Main renal artery narrowed to 1 mm. lumen by sclerotic plaque. *Micro:* Chr. pyelonephritis; mod. intrarenal arteriosclerosis; focal ischemic tubular atrophy.
7. W.F.	66 W M	180–240 / 100 140	2–8 months	Marked narrowing of arteries and moderate sclerosis.	*I.V.* No dye excreted by left kidney *Ret.* normal bilaterally. *Size: Left:* 10 cm.; *Right:* 11 cm.	47	1.016	0	33%	Nephrectomy, left, 9/27/54	18	120 / 80	60	20%	Moderate arteriosclerosis; otherwise normal.	*Weight*—63 gm. *Gross:* Very thin cortex; medulla normal. *Micro:* Cholesterol emboli in medium sized arteries; moderate intrarenal arteriosclerosis; widespread ischemic tubular atrophy; focal areas of pyelonephritis.
8. W.K.	61 W M	170–200 / 110 120	6 months	Slight blurring of discs; marked arterial narrowing; many hemorrhages and exudates	*I.V.* No dye excreted by left kidney. *Ret.* Normal bilaterally. *Size: left:* 9 cm.; *Right:* 13.5 cm.	37	1.020	1+–3+	65%	Nephrectomy, left, 4/13/55	14	110–120 / 70 80	29	56%	Normal	*Weight*—60 gm. *Gross:* Thinned cortex but normal medulla; main renal artery lumen reduced to less than ½ normal size by sclerotic plaque. *Micro:* Severe and widespread ischemic tubular atrophy. Moderate intrarenal arteriosclerosis.
											Died suddenly 15 months after nephrectomy of probable coronary occlusion. No autopsy.					
9. L.F.	34 C F	180–260 / 120 140	180 systolic for 5 years; abrupt change to severe hypertension for 8 months.	Retinal edema; marked narrowing of arteries and a-v compression; many hemorrhages	*I.V.* No dye excreted by right kidney. *Ret.* Normal bilaterally. Kidney's equal in size.	37	1.020	2+	57%	Nephrectomy, right, 8/19/55	12	165 / 95	31	74%	Normal except slight arteriosclerosis.	*Gross:* Normal kidney. *Micro:* Focal ischemic tubular atrophy; slight intrarenal arteriosclerosis; one of large branches of main renal artery partially occluded by organized thrombus.
10. M.H.	52 W F	210–250 / 105 120	Mild hypertension 4 years; severe hypertension 2 years.	Moderate narrowing of arterioles and some a-v compression.	*I.V.* Prompt bilateral excretion of dye, but right kidney small. *Ret.* Normal bilaterally. *Size: Left:* 15 cm.; *Right:* 8.5 cm.	34	1.020	0	55%	Nephrectomy, right, 9/21/55	12	150–180 / 80 95	31	65%	Normal except moderate arteriosclerosis.	*Gross:* Measures 7.5 x 4 x 2 cm. Cortex thinned, medulla normal. *Micro:* Chr. pyelonephritis, minimal intrarenal arteriosclerosis. Many wedge-shaped areas of ischemic tubular atrophy.

* In every patient with a non-functioning kidney, the opposite kidney was normal by i.v. pyelogram.

† These cases reported in previous communication (Ref. 8).

‡ Maximum specific gravity by Fishberg concentration test.

§ Kidney size represents the measurement from upper to lower pole of the kidney on the pyelogram films.

in nine patients and a *normal* collecting system was visualized in the non-functioning kidney in seven individuals. The latter finding strongly suggested that a renal vascular accident had occurred and was responsible for the absence of function. It seemed significant, in this series at least, that every patient (Nos. 1, 2, 5, 7, 8, 9, 10) with a normal calyceal pattern on retrograde study of the kidney that was not secreting urine, histologic examination of the same organ following nephrectomy revealed widespread evidence of "ischemic" tubular atrophy without any of the dilated thyroid-like tubules so characteristic of advanced pyelonephritis (cf. Part III). On the other hand, when pyelonephritis was the cause of the complete loss of renal function (patient No. 3), a distorted collecting system was seen on the retrograde study (18).

Abdominal aortograms were not performed in any of these patients. Undoubtedly, vascular defects of the renal arterial system would have been demonstrated by this procedure in some instances. However, aortography involves considerable risk (19) and since nephrectomy was to be carried out regardless of any findings on arteriography, this procedure was not performed.

Other studies of renal function: Total renal function was considered adequate when each of the following requirements was present; 1. urine specific gravity of 1.020 or better on concentration test, 2. phenolsulfonphthalein excretion of 55 per cent or greater in two hours, and 3. fasting blood non-protein nitrogen of less than 40 mg. per cent.

Five patients (Nos. 2, 3, 5, 6, 7) in the group failed to fulfill one or more of these criteria, indicating some diminished function in the "good" kidney in each individual. The most conspicuous impairment was seen in two subjects (Nos. 6 and 7) who had a mild degree of azotemia associated with greatly reduced phenolsulfonphthalein excretion.

Course following nephrectomy: Every patient in the group had a marked fall in blood pressure following removal of the non-functioning kidney. In eight individuals (Nos. 1, 2, 3, 6, 7, 8, 9, 10), the improvement was sustained during follow-up periods ranging from twelve months to four and one-half years; one patient (No. 2) relapsed 30 months after operation. The remaining two cases (Nos. 4 and 5) derived no lasting benefit from nephrectomy, since blood pressure readings returned to preoperative levels within six to eight weeks following surgery.

The relief obtained in eight patients was very striking as manifested by the reduction in blood pressure and disappearance of symptoms. Five of these subjects showed an occasional reading of 160/100–180/110 after operation, usually when under stress of some kind; but resting levels were never greater than 160/90. It is noteworthy that three of the latter patients (Nos. 1, 2, 9) had had mild blood pressure elevations (150/90–160/110) for several years before the development of severe and rapidly progressing hypertension that led to nephrectomy. In this group, removal of the functionless kidney resulted

in a reduction of blood pressure to the levels present *before* the onset of the severe hypertensive state (the phase that was presumably initiated by unilateral renal disease). Therefore, it was not unexpected when elevated readings were occasionally found in these three individuals following operation (similar to the postoperative course of patient S.B., Group C, Part I).

Another of the more impressive indices of benefit was the improvement in the fundoscopic findings. In every instance (Nos. 2, 6, 7, 8, 9) where marked changes were present preoperatively, the vascular spasm, papilledema, hemorrhages and exudates disappeared after nephrectomy.

The response of the five subjects who had manifested some reduction in *total* renal function was of particular interest. Following removal of the nonfunctioning kidney, four of the group showed remarkable improvement in their hypertensive state. Especially instructive were the findings in the two individuals with the most marked renal impairment (Nos. 6 and 7)—eighteen months postoperatively, blood pressure readings were 160/90 and 120/80 respectively, yet repeated renal studies performed at this time revealed the same degree of diminished function that had existed before the operation. With one exception (case No. 2), neither improvement nor deterioration in the function of the remaining kidney was observed in any patient following nephrectomy.

The only patient (No. 2) whose hypertension recurred, had enjoyed a period of remarkable benefit which lasted for two and one-half years. The return of the severe hypertensive state was accompanied by a low-grade but persistent azotemia. The relapse was not surprising and had been anticipated on the basis of the following observations: [1] Histologic examination of the kidney removed from this patient[9] at the original operation had revealed many cholesterol emboli occluding the medium-sized intra-renal arteries with associated tubular atrophy (8). It seemed inevitable that the remaining kidney would eventually be involved by the severe vascular disease which had led to the atheromatous embolization of the opposite kidney. [2] The patient had two documented episodes of urinary tract infection (inadequately treated) in the postoperative period. Pyelonephritis might also have contributed to the exacerbation of the hypertension.

Some observations in the two individuals (Nos. 4 and 5) who did not benefit should be noted. Patient No. 4 had the mildest degree of hypertension in the entire group and never exhibited the severe, rapidly progressing disease characteristic of those who improved after nephrectomy. The history of the recent surgical procedure on one kidney immediately preceding the onset of hypertension (occasionally a helpful diagnostic point (8) (20)) was presumably a fortuitous occurrence in this case, and unrelated to the hypertension.

[9] The clinical and pathologic data on this patient have been recorded in a previous communication (Ref. 8—Case No. 6).

The other patient (No. 5) who did not benefit from nephrectomy had manifested severe hypertension longer than anyone in this group (readings of 230/150 were obtained 6 years before nephrectomy). The excised kidney showed histologic evidence of decreased arterial flow and improvement was anticipated. Two factors that might have contributed to the lack of benefit were the prolonged duration of the severe disease (analogous to the irreversibility of hypertension following the removal of some pheochromocytomata (21)) and the possibility that ischemic involvement of the opposite kidney was present.

The single feature that seemed to offer the best explanation for the unusually high incidence of improvement in the group was the histologic evidence indicating reduced arterial flow in nine of these functionless kidneys.

PART III

Anatomical Observations in the Kidneys Removed at Operation

At the outset of our observations on patients whose hypertension was treated by unilateral nephrectomy, we attempted to correlate the histologic appearance of the removed kidney with the clinical results. It was predicted early, and subsequent events seem to substantiate our prediction, that the most important change in those kidneys responsible for hypertension would be that of convoluted tubular atrophy regardless of the cause. Our original cases had been of a *primary* vascular nature (8). Later, however, it became obvious that some of the cases were combinations of pyelonephritis and vascular disease, the latter being a common complication or even an essential part of advanced pyelonephritis. We also suspected that occasionally no histologic alteration of any kind would be observed. Goldblatt originally showed that the kidneys of his dogs with sustained hypertension induced by bilateral renal artery compression usually showed no tubular changes microscopically. Only with very severe arterial constriction, often leading to uremia and death, would tubular alterations consistently result (1-a). Indeed in one of our earlier cases, in whom the postoperative clinical course was highly successful, no renal tubular atrophy was found in the excised kidney (8). In certain experimental animals other than dogs, however, when only one kidney was made ischemic and sustained hypertension resulted, histologic examination of that kidney usually showed significant tubular atrophy (22). It thus seemed reasonable to assume that in a majority of human patients with unilateral renal disease leading to persistent hypertension some tubular atrophy would be present in the offending kidney.

We also believed that, in order to function as an endocrine organ of sufficient activity to result in hypertension, the cells of the atrophic tubules must nevertheless be of reasonable size and apparent viability. Completely atrophic cells as in advanced hydronephrosis and pyelonephritis, or dead tubular cells

within renal infarcts could not be functional. This concept has an experimental basis. Cash has shown that the transient rises of blood pressure, observed in his animals with surgical reduction of renal tissue and renal artery constriction, did not depend on the necrotic tissue (23). Removal of *totally infarcted or completely atrophic* kidneys therefore would not be expected to alleviate hypertension. Renal infarcts are commonly found at post mortem examination. Most of these infarcts have a relatively sharp line of demarcation between the necrotic and normal tissue, suggesting that the ischemia is usually limited to the zone of necrotic and completely non-functioning cells. This fact probably accounts for the rarity with which renal infarcts lead to persisting hypertension, since remaining ischemic *but viable* renal parenchyma is probably essential for the excessive production of the substance causing hypertension.

These postulates are also supported by autopsy observations. It has been our experience that post mortem study of individuals who had had sustained hypertension of either renal origin or the so-called "essential" variety there always was morphological evidence of impaired blood flow to significant areas of renal tubules. It has also been noted many times that a completely atrophic kidney might be seen in a patient without a clinical history of hypertension.

For many reasons we believed that study of the renal vascular bed would not provide information to allow prediction as to the success of the nephrectomy. In surgically removed kidneys, the entire renal vascular tree is not available for study since the aortic orifice and the proximal two or three centimeters of renal artery are not removed. Therefore a consistent estimate of the impairment of blood flow by study of the vascular tree would not be possible. The importance of that proximal portion of the renal vascular bed in producing hypertension has been emphasized by Blackman (24). It has been repeatedly shown that the vessels in a kidney made ischemic by various means appear to be protected from the effects of hypertension and, indeed, may be the only vessels in the body spared. Also, in advanced nephritis of any type the intrarenal arteries usually show severe intimal proliferation and luminal obstruction, yet the tubules will be completely atrophic and presumably quite functionless. In our cases, the arteries were either normal or showed intimal arteriosclerosis of varying severity. The arterioles were either hyaline as in hypertension of any cause or were normal.

The condition of the glomeruli was also unimportant, although in the cases of pure vascular disease the glomeruli were usually remarkably well preserved. Glomerular cells probably are not the complex functional units that the convoluted tubule cells are and may not be injured by moderately severe ischemia. The glomeruli of our cases were either normal, showed the pericapsular fibrosis thought to be characteristic of pyelonephritis, or occasionally were massively scarred.

In applying our hypothesis that the presence or absence of significant tubular atrophy would allow prediction as to the result of nephrectomy upon hypertension, it was obviously necessary to have a selected series of patients. If all individuals with hypertension were studied, the incidence of bilateral renal disease would be infinitely greater than unilateral. The prediction of success in the therapy of hypertension on removal of one kidney in such an unselected series would be impossible. Yet in a series selected by choosing those hypertensive individuals with obvious disease in one kidney in whom nephrectomy was performed, application of the hypothesis seemed to have value in estimating prognosis.

Three or four large sections of renal cortex were studied with the hematoxylin and eosin stain. In those cases showing significant areas of *atrophy of the convoluted tubules of the "ischemic" type*, the cells of which were nevertheless apparently viable, success in the treatment of the hypertension was predicted (Figs. 2, 3, 4, 5). The quantity of the altered renal tubules also seemed important for occasionally islands of this "ischemic" tubular atrophy were present in such trivial amounts as to make it questionable whether the hypertension was a consequence. This "ischemic" atrophy is quite different from the dilated thryoid-like tubules with exceedingly tiny epithelial cells seen in advanced pyelonephritis, particularly when hydronephrosis was marked (Fig. 6). When the excised kidney disclosed only these dilated thyroid-like tubules

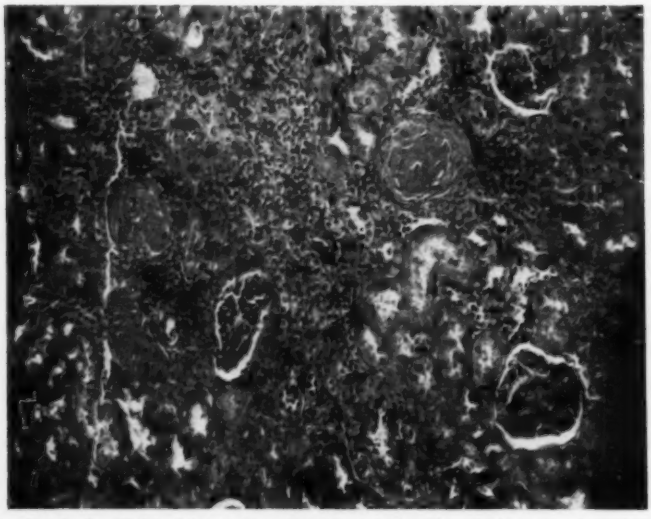

FIG. 2 (Pt. S. B., Table V). Areas of marked ischemic tubular atrophy of the typical appearance lying between normal renal tubules. Benefit was predicted.

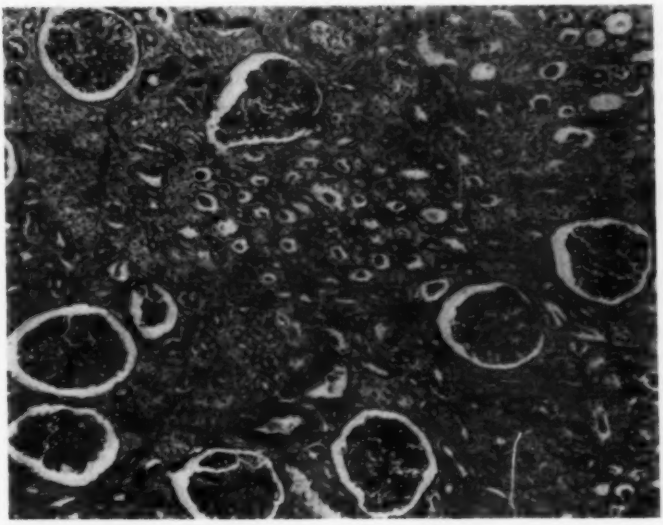

FIG. 3 (M. P., Pt. No. 1, Table IX). Marked atrophy of tubules of the ischemic type with resulting condensation of glomeruli.

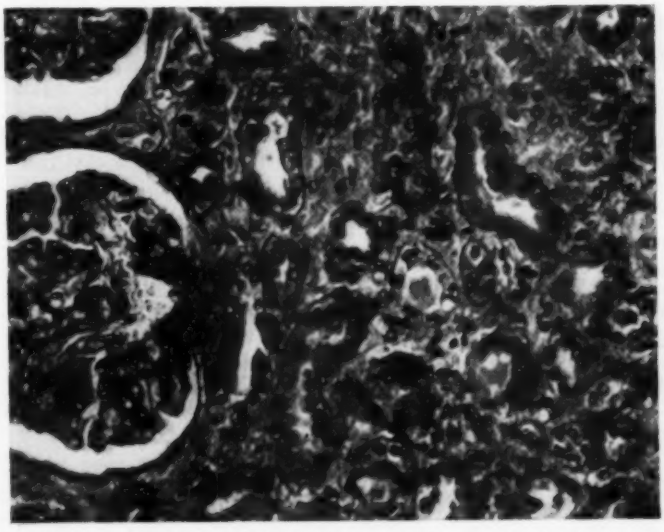

FIG. 4 (M. P., Pt. No. 1, Table IX). This shows high power magnification of the ischemic renal tubular atrophy. Note normal glomeruli and atrophic but still "healthy" appearing tubular cells.

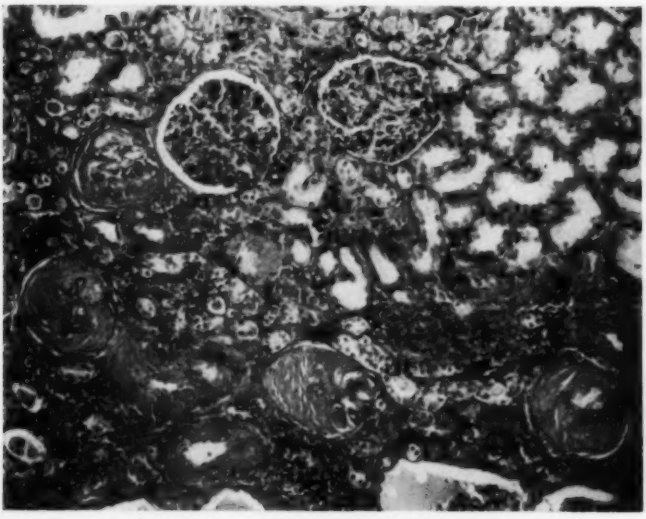

FIG. 5 (Pt. R. E., Table IX). Foci of ischemic tubular atrophy as well as normal renal tubules. On left, atrophic tubules with casts are seen. Other areas of this kidney showed more advanced changes of chronic pyelonephritis. Benefit was predicted.

(Part I, Group D), no improvement of hypertension followed nephrectomy. The important atrophic tubules were formed by small cuboidal epithelial cells often with clear cytoplasm and frequently with very small or even imperceptible tubular lumina. This type of simple tubular atrophy (Figs. 2, 3, 4, 5) was thought to be the consequence of ischemia. Because of the tubular atrophy, the glomeruli were often close together and many more were visible in each microscopic field than in normal kidneys or in normal areas of the damaged kidney. *The "ischemic" tubular atrophy* is typically seen at the *borders* of infarcts. It is commonly found in arteriosclerotic nephritis and is seen in both glomerulonephritis and pyelonephritis, though not as consistently in the latter as in the former. In all of these conditions it is probably the result of reduced blood flow either as a consequence of the associated vascular disease or the scarring of the glomeruli through which most renal tubular blood must flow. We believe that this type of tubular atrophy is the only significant morphological renal lesion that can be correlated with all types of renal hypertension. As previously mentioned, it may be absent even though the hypertension is a consequence of renal ischemia. The coexistence of this type of tubular atrophy and hypertension has also been described recently in chronic pyelonephritis by Kincaid-Smith (25). In our series of 21 cases, the presence of significant areas of this type of tubular atrophy made it possible to predict correctly the alleviation of hypertension following nephrectomy in 14 of 15 cases. The one case in which we were not

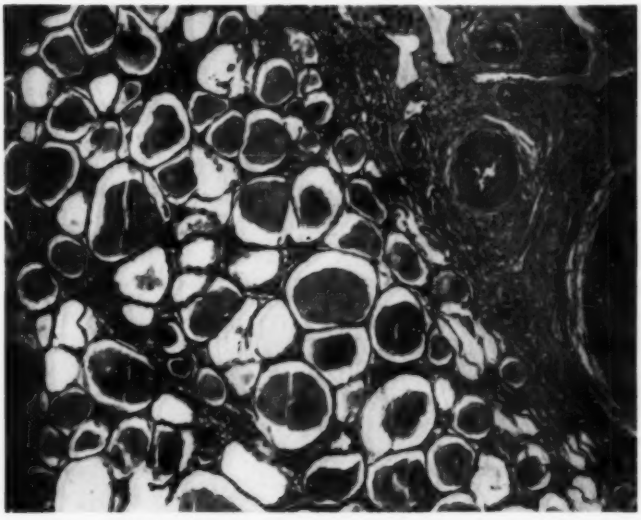

FIG. 6 (Pt. B. H., Table VI). The classical appearance of advanced chronic pyelonephritis with thyroid-like tubules and extreme atrophy of the tubular epithelium. In spite of marked vascular disease no benefit from surgery was predicted.

able to give the correct prognosis had no morphological lesions in the resected kidney except, perhaps, hyperplasia of the juxtaglomerular apparatus. Of the six surgical failures, we predicted the failure in four since there was an absence of this type of tubular atrophy. We were wrong in the other two, for, in spite of the presence of the typical small atrophic tubules, the hypertension was not cured by nephrectomy. These two patients had had severe hypertension for more than six years and probably vascular changes were already irreversible in the remaining kidney.

A biopsy of the kidney would be of doubtful value in predicting the effect of nephrectomy on hypertension. In many of the cases, large areas of the renal cortex were completely normal while in other cases with pyelonephritis, areas of dilated, completely atrophic thyroid-like tubules were interspersed among areas of ischemic tubular atrophy. It would be pure good fortune to obtain areas of the apparently significant tubular changes by biopsy.

DISCUSSION

The experimental observations of Goldblatt[10] (1), Pickering and Prinzmetal (26), and Wilson and Byrom (22) offered irrefutable evidence that in some

[10] Goldblatt produced only transient hypertension in the dog following the constriction of one renal artery. Whereas in other experimental animals (22, 26) partial constriction of one renal artery produced sustained hypertension.

animals, reduced arterial flow to one kidney can be an important factor in the genesis of hypertension.

The existence of a similar mechanism for hypertension in man seemed dubious in view of the infrequent lowering of blood pressure that followed the removal of a "diseased" kidney from hypertensive individuals. This fact was emphasized in Smith's critical review of the subject in 1948 (3). He collected 242 patients from the medical literature and found that nephrectomy produced sustained relief of hypertension in only 20 per cent of the cases. These results led Smith to the pessimistic conclusion that "the advisability of nephrectomy must rest upon conservative and recognized *surgical* indications and not upon the hope of reducing blood pressure" (3). Thompson and Smithwick (27) expressed similar views. Pickering and Heptinstal (28) and Rosenheim (29) noted alleviation of hypertension in only 30 per cent of their cases following nephrectomy.

In most of these published reports it was not possible to determine the incidence of reduced arterial flow in the kidneys that were removed. Yet, in those situations wherein unilateral renal ischemia was *clearly* demonstrated, nephrectomy invariably resulted in relief of hypertension (8, 30, 31).

The study of urine simultaneously obtained from each ureter in hypertensive subjects as described in Part I of this report appears to provide a relatively simple functional test that will determine when disease in one kidney is responsible for hypertension. Thus far, at least, the test has proven accurate with an impressive degree of predictability as to the effect of nephrectomy on blood pressure.

Ureteral Catheterization Studies: At the beginning of this study the authors were disturbed by the possibility that mechanical or reflex changes produced by the introduction of catheters to the kidney pelves might alter renal function, influencing one side more than the other, thus vitiating the results. The observations in the patients with "essential" hypertension (Group A) wherein urine volume and electrolyte concentration from the two kidneys were nearly identical, gave considerable assurance that the catheters *per se* had not disturbed function, or if they had, the direction and degree of alteration were the same on the two sides. Similar studies on individuals with bilateral renal disease (Group B) supported this supposition. In this latter group, a significant reduction in urine volume on one side (*without* a concurrent lower sodium concentration) was occasionally observed. In no instance did the functional pattern suggest decreased blood flow to *one* kidney as defined by the experiments of White and co-workers (10, 11).

An appraisal of the diagnostic value of the test was afforded by the observations made on eight hypertensive patients with unilateral renal disease in whom nephrectomy was performed. In four instances (Group C) the hypertension was alleviated by the operation, while in the other four subjects

(Group D) extirpation of one kidney had no effect on blood pressure. In each group the ureteral catheterization studies revealed distinctly different results which accurately predicted the effect of the nephrectomy.

Equally significant in separating these two groups were the histologic findings observed in the excised kidneys. In Group C (patients benefited by nephrectomy) widespread areas of tubular atrophy (Figs. 2–5) were noted in three instances (R.M., S.B., N.T.). The kidney from the other patient (I.N.) disclosed no gross or microscopic abnormality, yet aortography had clearly shown a marked narrowing of the main renal artery in this individual. Another observation of interest was the microscopic evidence of a considerable degree of chronic pyelonephritis in patient N.T. (Similar to Fig. 5). In the kidneys removed from the other patients in Group C, a similar inflammatory process was not found. This suggests that pyelonephritis may have been directly responsible for the ischemic atrophy of the kidney removed from patient N.T. (since no major renal artery defect was demonstrated at operation). It may be well to suggest here that while the dilated thyroid-like atrophic tubules (Fig. 6) of chronic pyelonephritis are very probably the effect of the inflammatory disease and especially urinary obstruction, the small, often lumen-less atrophic tubules described in Part III (Figs. 2–5) are very likely purely of ischemic origin regardless of the cause of the ischemia. The recent observations of Kincaid-Smith (25), who noted widespread microscopic evidence of ischemia in kidneys from patients with pyelonephritis and hypertension, support this supposition.

Contrariwise, three cases in Group D (patients not improved by nephrectomy) showed histologic changes which were sharply at variance with the findings in those who benefited (Group C). A pyelonephritic process had destroyed most of the kidney and there was a virtual *absence* of the atrophic type of tubules indicative of reduced arterial flow (Fig. 6). The kidney removed from the remaining patient (V.H.) in Group D contained large segments of tubular atrophy similar to those observed in Group C, yet this individual derived no benefit from operation. The exact reason for the lack of improvement was not ascertained, but significant disease may have been present in the opposite kidney (this subject also had had *severe* hypertension for 7–8 years, longer than any c[illegible] in this entire series). However, the significant observation was the result obtained on the ureteral catheterization study (Table VI) which suggested that this kidney was not solely responsible for the hypertension and the postoperative course of the patient proved this prediction to be correct.

The authors believe that the "negative" tests in Group D are equally if not more important than those in Group C in evaluating the diagnostic worth of the catheterization studies and would be further reassured if more such data were available. The patients in Group E also gave "negative" results and

therefore nephrectomy was not performed. We may have missed an opportunity for considerable benefit of the hypertension in some of these individuals, but on the basis of the studies to date, removal of these kidneys *for relief of hypertension* did not seem justified.

Additional evidence enhancing the validity of these observations was gained by study of a patient with unilateral pyelonephritis and *normal* blood pressure (Table VIII, H.H.). Examination of the urine from the two kidneys gave results identical to those recorded in Group D (hypertension not improved by nephrectomy), which should have been expected, if in the latter group, the unilateral renal disease was unrelated to the hypertension. Correlating equally well were the microscopic findings in the kidney removed from this subject—the changes were indistinguishable from those observed in the patients in Group D with pyelonephritis (Fig. 6).

Interpretation of a "Positive" Ureteral Catheterization Test: The degrees of variation in water and sodium output which are significant have not been defined, i.e., how little difference in urine flow or sodium concentration must be present and still enable one to predict alleviation of hypertension after nephrectomy. Thus far, the patients with the smallest differences in the urine from the two kidneys who had a beneficial result from operation (Group C) showed at least a 60 per cent reduction in urine volume *and* a 15 per cent lowering of sodium concentration on the same side. It should be reemphasized that the "precautions", as enumerated in Part I, must be carefully observed in every patient in whom these studies are performed. The greatest danger in improper interpretation of the test lies in the lack of consideration of each of these pitfalls.

The experimental observations of White (10, 11) suggest that any narrowing of one renal artery which produced a detectable reduction in arterial flow always resulted in at least a 50 per cent decrease in urine flow from this kidney.[11] With increasing reduction in renal arterial flow, urine volume was lowered even more from this kidney, and the sodium concentration in this urine was likewise decreased. Therefore, it is currently believed that anything less than a 50 per cent reduction in urine volume from one kidney on the simultaneous catheterization study is probably not indicative of unilateral ischemia, even though urine sodium concentration may be reduced on this

[11] It seems worthwhile noting that constriction of the main renal *vein* to one kidney likewise may produce a 50 per cent reduction in urine volume from the ligated side when compared with urine obtained simultaneously from the opposite untampered kidney, as demonstrated by the animal experiments of Blake and associates (32). But sodium *concentrations* in the urine from the two sides were *identical* or slightly *higher* from the kidney with the vein ligation (even when venous pressure was increased to 500–600 ml. water). Thus the pattern obtained on the simultaneous ureteral catheterization study with ligation of one renal vein was distinctly different from that which resulted following the ligation of the main renal artery as described by White and his associates (11).

side. This is supported by the results of the catheterization studies in one severely hypertensive patient who had a consistent 25 to 30 per cent lowering of urine volume from one kidney with a 10 to 20 per cent lesser sodium concentration in this urine when compared with that obtained simultaneously from the opposite side. (Aortogram revealed a normal renal arterial system.) This kidney was later removed and the hypertension remained unaffected after a five month period of follow-up. Microscopic examination of this kidney revealed no abnormality.[12]

There is another situation that causes some concern in evaluating the results of this test. Chronic pyelonephritis may sometimes cause a functional defect which results in an excessive *loss* of sodium in the urine (33). If such a process should involve only one kidney and eventually lead to hypertension, will the urine from this kidney then reflect the functional pattern of decreased arterial flow in the simultaneous catheterization studies? This still remains a possible hazard in interpretation, but in four patients with hypertension and pyelonephritis subjected to nephrectomy, N.T. in Group C (who benefited) and 3 patients in Group D (who did not improve), the test correctly predicted the postoperative result in each instance.

Whether the ureteral catheterization test will continue to show such uniformly prophetic qualities must await further experience. When the studies are properly carried out, it is believed they should aid considerably in raising the incidence of improvement in hypertension following nephrectomy (3, 28, 29) and increase the recognition of unilateral renal vascular disease (25, 34).

Reports from other clinics lend confirmatory evidence to the value of these studies in detecting diminished arterial flow to one kidney in hypertensive individuals. In two patients (20, 31-a) the test showed a reduction in sodium concentration of 25 per cent or more in the urine from one kidney. Aortograms demonstrated an impaired arterial supply to the same organ. *Unfortunately coincident determinations of urine volumes were not reported.* Both patients were subjected to nephrectomy and relief of hypertension ensued.[13]

In another publication by Poutasse (35), ureteral catheterization studies were carried out in a 15 year old boy with severe hypertension associated with

[12] Though we have not seen, as yet, any normotensive patient with a simultaneous catheter study which we would interpret as indicating unilateral vascular disease, it is not inconceivable that such instances will be met. Dogs with unilateral renal artery constriction do not uniformly develop hypertension. The extraordinarily high incidence of so-called "labile blood pressure" (both before and after operation) in our series of patients with improvement after nephrectomy, suggests that there may be one or more adjuvant factors in the overall mechanism of their hypertension

[13] The authors are indebted to Dr. Tate Mason, Seattle, Washington, who allowed us to review histologic sections of the kidney removed from his patient (20). In one of these sections widespread areas of tubular atrophy of the "ischemic type" were present—identical with the pathologic findings noted in Table V of this paper.

stenosis of *both* renal arteries. *Again no urine volume measurements were reported.* Initial results revealed a 17 per cent lesser concentration of sodium in the urine obtained from the left kidney as compared with that secured from the opposite side. The left renal artery constriction was then surgically relieved by an arterial homograft. Repeat catheterization studies disclosed the sodium concentration in the urine from the right side was 40 per cent lower than that from the left. (The hypertension was not affected by this operation). Then the right renal artery stenosis was corrected by a similar grafting procedure with immediate alleviation of hypertension. Two weeks later, *identical* sodium concentrations were found in the urine obtained simultaneously from each kidney. Correction of the renal artery stenosis was convincingly confirmed by a postoperative aortogram, and the patient's blood pressure remained normal during the 3-month period of follow-up.

This account emphasizes additional points worthy of consideration in the study of hypertensive subjects. Occasionally in young people, hypertension may be due to a pathologic process that narrows both renal arteries. Ureteral catherization studies would be of no value in this situation, but aortograms should be diagnostic. In the therapy of renal vascular defects, when surgically feasible, arterial homografts are preferable to nephrectomy.

Indications for the Catheterization Test: The frequency with which hypertension is caused by disease in one kidney is not known. Smith (3) has estimated that in one out of every 200 hypertensive patients this mechanism may be responsible. The malady has not been uncommon at this hospital. In the past five years, unilateral renal disease as a cause of hypertension has been recognized ten times more frequently than has pheochromocytoma.

It is obviously impossible and unnecessary to carry out the catheterization procedure in every patient with high blood pressure. The test should be reserved for those hypertensive individuals who present some of the suggestive clinical features frequently evident when hypertension results from a unilateral renal vascular abnormality.

Clinical Features Observed in Patients with Hypertension Due to Unilateral Renal Disease: Fifteen patients have been studied at this hospital in whom removal of an ischemic kidney resulted in sustained relief of hypertension (12 cases in this report and 3 from a previous communication (8)). A review of the clinical records emphasized certain features which have assisted the authors in recognizing patients with hypertension of renal vascular origin. Some of these findings have been referred to previously in this report. A summary of these features seems appropriate at this point.

The most consistent manifestation in the history was the *abruptness of onset* and/or *rapid progression* of severe hypertension often presenting as the "malignant" form (as outlined in Part II). Similar findings have been stressed by

Perera and Haelig (16). Recent abdominal pain suggesting renal colic or appendicitis (with removal of a normal appendix at operation) soon followed by hypertension should arouse suspicion that a renal vascular insult may have occurred (8). A history of abdominal trauma, surgical (20) or accidental (8, 34), just preceding the onset of high blood pressure has been described. The age of onset of hypertension has sometimes given a clue. In eight of these fifteen patients, the elevated blood pressure appeared before the age of 30 or after the age of 55. It would be unusual for severe *essential* hypertension to *begin* at this time of life (36).

The physical examination usually offered no differential diagnostic assistance, the findings being typical of those seen in severe essential hypertension. The fundoscopic examination often indicated advanced changes and papilledema was present in about 50 per cent of instances.

Some of the important x-ray findings have been recorded in Part II. In addition it was significant that four of the fifteen subjects had intravenous pyelograms indicating *normal kidney size and calyceal outlines and no impairment of function in either kidney*. More frequently, however, the "diseased" kidney was one to three centimeters smaller than the opposite one. Aortograms were carried out in only three of these fifteen patients, and in each instance unilateral renal arterial defects were demonstrated. This latter procedure is helpful but not essential in diagnosis.

Studies of *total* renal function usually indicated adequate reserve, but occasionally significant impairment was noted. Previous investigators (1, 3, 28, 37) have emphasized that if patients with hypertension and unilateral renal disease showed impaired function in the opposite kidney, nephrectomy was contraindicated. We have observed two patients (Part II, Nos. 6, 7) who had definite evidence of *bilateral* reduction in renal function in whom removal of one functionless kidney alleviated the hypertension without affecting the function in the remaining kidney. A more striking instance has been reported by Imber and Clymer (30) wherein removal of an ischemic kidney from a patient with severe hypertension, azotemia, albuminuria, and hyposthenuria resulted in a return of blood pressure to normal and a *disappearance* of these renal abnormalities.

Following nephrectomy some of these patients continue to show some lability of blood pressure. Pickering and Heptinstall (28) have reported similar results in patients relieved of hypertension after the removal of a diseased kidney.

It has been stated (37) that removal of a diseased kidney was unlikely to affect blood pressure in individuals whose hypertension had existed for more than two years. In four of the patients in this series who were benefited by nephrectomy, severe hypertension had existed for two years or more before

the operation. Even more impressive was the report of Rosenheim (29) wherein removal of one kidney from a patient resulted in relief of severe hypertension that had been present for *seven* years.

Two of the fifteen patients herein reported who benefited from nephrectomy died fifteen months following operation, of cerebral and probable coronary vascular accidents respectively. Only one patient (Part II, No. 2) has had a recurrence of hypertension. The other twelve individuals remain well during follow-up periods ranging from one to fifteen years.

SUMMARY

This report contains a review of the experience by the authors in the attempted relief of hypertension by removal of single abnormal kidneys. In a series of 21 patients, examination of the kidneys from the fifteen who improved disclosed histologic changes thought to be the consequence of reduced blood flow in 14 instances; in the single exception where the removed kidney demonstrated no evidence of tubular atrophy, arteriogram had disclosed a narrowed renal artery. In the six patients not improved by nephrectomy, the removed kidney did not show the ischemic type of tubular atrophy in 4 instances. This experience affords further evidence that the Goldblatt phenomenon is applicable to man, and that reduced arterial flow to sizable segments of renal parenchyma can induce hypertension.

Studies of simultaneously collected urine from each kidney have proven to be of value in distinguishing those abnormal kidneys which are responsible for hypertension from those which are not. Where there has followed improvement from nephrectomy, there has thus far been found invariably a lesser urine flow and reduced sodium concentration in that urine when compared with urine collected from the opposite side. Contrariwise, patients unimproved by nephrectomy have not exhibited these changes, nor have patients later proven to have *bilateral* renal disease.

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STUDIES ON THE PATHOGENESIS OF FEVER

VII. Comparative Observations on the Production of Fever by Inflammatory Exudates in Rabbits and Dogs[1]

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Heat-labile, fever-promoting materials are present in extracts of rabbit polymorphonuclear leukocytes and in the exudates of acute pleural and peritoneal inflammations produced by infusions of 0.85 per cent NaCl solution (hereafter referred to as "physiologic saline") in that animal (1, 2). These observations focussed attention on the leukocyte as a possible source of pyrogenic substances in disease states. Extensive investigations of other tissues of the rabbit failed to disclose the presence of extractable fever-producing substances. The discovery of a transferable secondary pyrogen in the serum of rabbits after intravenous injection of typhoid vaccine (3, 4) raises the possibility that these endogenous pyrogens in the rabbit are qualitatively similar.

The present studies were undertaken to search for thermogenic substances of endogenous origin in another animal species. This report describes the properties of fever-producing substances in canine exudates and summarizes comparative studies indicating a species-specific activity of pyrogenic tissue products.

MATERIALS AND METHODS

Animals. Male and female mongrel dogs weighing 6–10 Kilos and male rabbits of mixed breed and color weighing 2–3 Kilos were used.

Production of Exudates. Rabbits were tied on their backs, their abdomens shaved, and 300 ml. of physiologic saline containing no antibiotics were infused into the peritoneal cavity by constant drip over a period of about three hours. Animals were then kept recumbent for an additional 3 to 4 hours, anesthetized with pentobarbital, and the abdomen was opened through a mid-line incision through which the remaining fluid was aspirated into 250 ml. centrifuge bottles. Samples were cultured in thioglycollate broth and exudates were stored at 4°C. Ten ml. aliquots were injected intravenously into normal rabbits. When febrile responses occurred in test animals, fluids were re-tested after heating at 90°C. for 30 minutes, a procedure which is necessary to rule out contamination by ordinary bacterial pyrogens (1).

Intraperitoneal infusion of physiologic saline consistently failed to elicit a polymorphonuclear leukocyte response in dogs and intravenous injection of large quantities of cell-free fluids collected after this procedure into normal dogs produced no fevers. Therefore several

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irritants were added to the infusion, including starch, kaolin, talc, glycogen, turpentine suspended in alcohol, and Aleuronat (Bios Laboratories). Results with most of these were inconsistent; the most satisfactory exudates followed injection of Aleuronat although turpentine-alcohol-saline mixtures occasionally resulted in heavy exudation. The procedure finally employed was as follows: Dogs were anesthetized with pentobarbital and a suspension of 10 grams of Aleuronat (which had been baked at 170°C. for 3 hours, did not produce fever when injected into rabbits intravenously, and was bacteriologically sterile) in 100 ml. of physiologic saline was injected intraperitoneally through an 18 gauge needle. Twenty-four hours later, animals were again anesthetized and 1500 ml. of physiologic saline were infused into the peritoneal cavity through a 15 gauge needle, over a 30 minute period. Four hours later the abdominal fluid was removed through a trochar inserted into the flank. This technique diminished the incidence of contamination of the fluids which, in the dog, was very high when aspiration through an abdominal incision was attempted. Fluid was aspirated directly into 250 ml. centrifuge bottles, total leukocyte counts were performed immediately, and samples were cultured in thioglycollate broth at room temperature and 37°C. The usual yield was 600–1000 ml. of slightly turbid fluid which was stored at 4°C. Several exudates were divided into two parts; one-half was centrifuged at 2000 RPM for 30 minutes, the supernate was decanted, and the centrifugate was ground in a Ten Broeck apparatus after addition of 5–10 ml. of physiologic saline. The ground sediment was resuspended in 60–100 ml. of physiologic saline and both supernatant fluid and sediment were stored at 4°C. until tested in animals.

All tests were carried out within 7 days after preparation of the exudates with the exception of the experiment in which several fluids were pooled in order to study the effects of repeated injections.

Preparation of Leukocyte Suspensions. Intramuscular deposition of 1–2 ml. of turpentine into normal dogs results in sterile abscesses at the site of injection and marked elevation of the peripheral leukocyte count (5). Donor dogs treated in this fashion were exsanguinated when the circulating leukocytes reached 40,000/mm³ or higher. Attempts to prepare suspensions of white cells by means of differential sedimentation in bovine albumin (Armour Laboratories) or fraction I (6, 7) were not feasible because of the risk of bacterial pyrogen contamination. Therefore, with heparin or sodium sequestrene as anti-coagulants, blood was centrifuged at 3500 RPM for 1 hour and the buffy coat removed by gentle suction. The white cells were then resuspended in 10–20 ml. of physiologic saline and counts were performed. Concentrated white cell suspensions obtained by this method contained about 100 to 200 thousand cells/mm³, although clumping made accurate enumeration difficult.

Preparation of Vaccine. A formalin killed *Alkaligenes fecalis* vaccine containing 3×10^9 bacteria/ml. was used in experiments in pyrogen tolerance.

Testing of Samples. Whole exudates, supernatant fluids and resuspended sediments were tested for ability to produce fever by intravenous injection of 5–10 ml. amounts in rabbits and 20–100 ml. in dogs.

Recording of Temperatures. Rabbits were placed in metal stalls, secured by loose-fitting collars, and after periods of acclimatization in the stalls, several baseline recordings of body temperature were obtained by means of resistance coils which remained in the rectum throughout the experiment. After injection of test materials, temperatures were recorded at intervals of 30 minutes for four hours.

Dogs were unrestrained in cages and food and water were withheld on the day of an experiment. Rectal temperatures were taken with ordinary clinical thermometers at 30 minute intervals for four hours after injection of test materials. All fever curves were plotted on standard graph paper and the "fever index" determined. (8).

Avoidance of Contamination by Bacterial Pyrogens. Rigid precautions were used to prevent contamination by ordinary bacterial pyrogens. These have been described in detail elsewhere (1).

RESULTS

The Relationship of Thermogenicity to the Presence of Leukocytes in Sterile Peritoneal Exudates. Sterile peritoneal fluids obtained from 33 dogs were examined; in 22, Aleuronat had been used as a peritoneal irritant, turpentine and alcohol had been added to the infusate in six animals, and other adjuvants had been employed in the other five. Leukocyte counts of these fluids ranged from 300 to 16,000/mm³ with a mean of 3300/mm³. One-third of the fluids failed to produce significant fever when injected intravenously into normal dogs in volumes of 20 and 50 ml. Because the febrile responses observed with 20 or 50 ml. of each of the remaining fluids were not appreciably different in magnitude, the results were combined for purposes of analysis. There was considerable variation in the ability of the different exudates to produce elevation of temperature but this bore little relation to the number of cells present in a fluid (Fig. 1). In general, however, exudates produced by Aleuronat

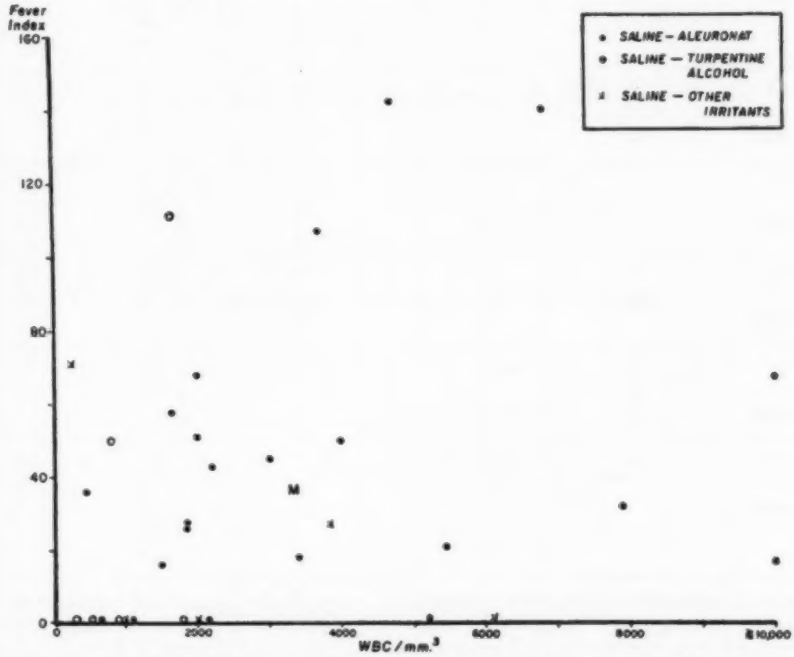

FIG. 1. The relationship between the febrile responses of dogs injected with sterile peritoneal exudates and the leukocyte content of fluids.

TABLE I

Febrile Responses in 93 Dogs Injected with Sterile Peritoneal Exudates

Exudate No. and Wbc.	Unspun Exudate				Supernate				Sediment			
	Unheated		90°C.		Unheated		90°C.		Unheated		90°C.	
	No. Animals	Fever Index	No. Animals	Fever Index	No. Animals	Fever Index	No. Animals	Fever Index	No. Animals	Fever Index	No. Animals	Fever Index
71 15000	4	66 32 51 117	2	0 0	3	51 40 72	2	0 0	2	28 166	2	0 10
5C 4000	3	151 0 0	—	—	3	59 33 0	—	—	2	22 10	—	—
78 1650	—	—	—	—	2	10 10	—	—	2	68 48	2	0 10
60 3500	3	84 27 20	—	—	1	33	—	—	5	50 89 15 100 81	1	0
5B 2000	3	79 12 62	—	—	2	75 15	1	0	3	114 61 10	1	56
57 5200	—	—	—	—	1	111	—	—	2	252 293	1	22
5A 2200	2	0 101	—	—	1	10	—	—	2	147 93	3	51 37 14
Y 1850	3	36 10 32	1	0	3	42 87 10	1	0	2	187 137	2	0 32
72 3400	1	18	1	0	1	66	1	0	5	158 81 79 120 53	2	33 0
Fever Index	Mean for 19 tests = 42		Mean for 4 tests = 0		Mean for 17 tests = 43		Mean for 5 tests = 0		Mean for 25 tests = 99		Mean for 14 tests = 19	

were richer in polymorphonuclear leukocytes and more pyrogenic than those elicited by the other irritants.

Fever-producing Capacity of Fractionated Peritoneal Exudates. Peritoneal fluids from 9 dogs were partitioned and the ability of whole exudate, resuspended sediment, and supernatant fluid to produce fever in normal recipient dogs was determined. The results are detailed in Table I and presented graphically in Figure 2. Although whole exudate and supernatant fluids produced fever in 90 per cent of the test animals, the responses were generally small. In contrast, resuspended sediments were potent pyrogens. In all cases, heating of the exudate, supernatant fluid or sediment at 90°C. for 30 minutes eradicated or markedly diminished the fever-promoting effect. Again, there was considerable variation in the febrile responses of individual animals given samples of identical material. In most cases 20 ml. quantities were tested but in several

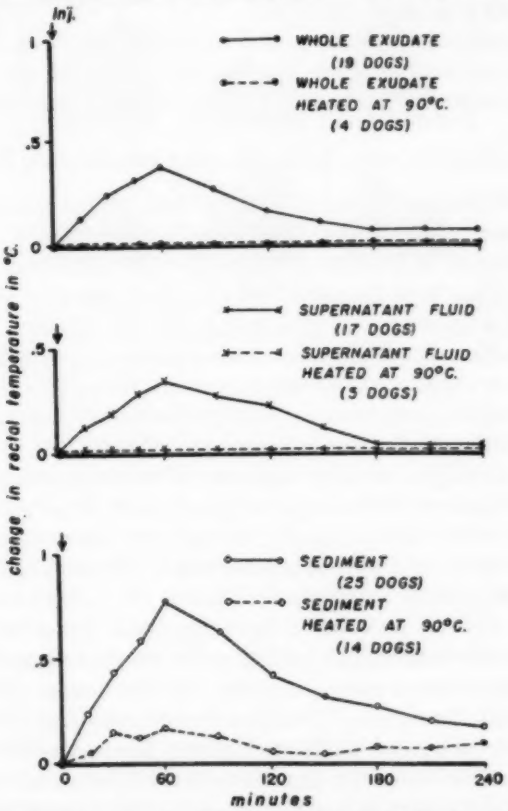

FIG. 2. Mean temperature records of 93 dogs injected with fractions from canine peritoneal fluids.

animals, 50 and 100 ml. were injected and gave essentially the same amount of fever.

Effect of Canine Exudates in Rabbits. Five or 10 ml. aliquots of 22 pyrogenic canine exudates were administered intravenously to 56 rabbits. Only 2 rabbits responded with a rise in temperature, and repeated testing of these fluids in other rabbits resulted in no fever. It was concluded that canine peritoneal exudates which are capable of producing fever in dogs are inactive in rabbits. Supernatant fluids and resuspended sediments also failed to evoke febrile responses in rabbits.

Inability of Peritoneal Exudates from Rabbits to Produce Fever in Dogs. Twelve normal dogs received intravenous injections of 20–100 ml. of sterile peritoneal exudates prepared in rabbits. None of the recipients responded with a rise in temperature, although these fluids were potent in eliciting fever in normal rabbits in doses of 5.0–10 ml.

Effect of Leukocyte Suspensions Obtained from Whole Blood. Ten normal dogs received suspensions containing between 1.2×10^8 and 3.2×10^{12} wbc. by the intravenous route. None showed a rise in body temperature.

Comparison of Canine Tissue Pyrogens with Bacterial Endotoxins

A. Effect of heating. As has been mentioned, peritoneal exudates obtained from dogs were rendered non-pyrogenic by heating at 90°C. for 30 minutes. This is in contrast to bacterial endotoxins which withstand boiling or autoclaving (9). It has been demonstrated that small amounts of bacterial endotoxins mixed with serum are also inactivated by exposure to 90°C. for 30 minutes (10). However, when toxins were added to sterile peritoneal exudates, heating did not abolish their ability to produce fever. This supports the idea that, in the absence of serum, heat-lability of a tissue extract is solid evidence against contamination by bacterial pyrogens.

B. Tolerance. Repeated daily injection of bacterial pyrogens into rabbits results in resistance to the fever-producing effect (8). This "pyrogen tolerance" also develops in man and in dogs (9). On the other hand, repeated injection of peritoneal exudates in rabbits does not result in tolerance (2).

In the present study centrifuged sediments from 17 canine exudates were pooled. The resulting fluid was a potent pyrogen. Three normal dogs were given daily intravenous injections of 20 ml. of the pooled exudate, rectal temperatures being recorded every other day. The fever curves, shown in Figure 3 were comparable throughout, indication that the recipient animals developed no tolerance to the exudate's pyrogenic action. The mean fever index for the 3 animals on the first day of the study was 206 and 268 on the tenth day.

In contrast, daily intravenous injection of 1 ml. of *A. fecalis* vaccine, resulted in typical resistance to its fever-producing effect (Fig. 4, Day 2 and 10). In the

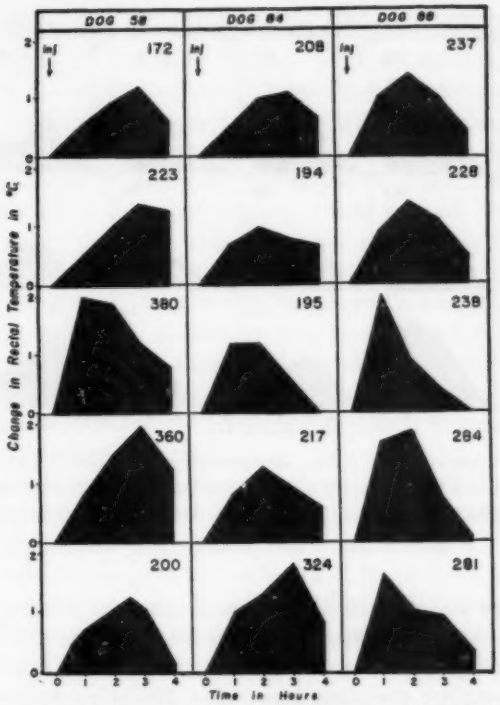

FIG. 3. Fever curves of 3 dogs given 20 ml. of exudate daily for 10 days. Numbers represent fever indices. Note that the temperatures of each dog on the first, third, fifth, eighth and tenth day are approximately the same and that tolerance does not develop.

course of nine days the fever index for three animals decreased from 280 on the first day to 108 on the 9th day.

Failure to Demonstrate Cross-tolerance between Bacterial Pyrogens and Peritoneal Exudates. A well-known characteristic of tolerance to bacterial endotoxins is its non-specificity; animals resistant to one bacterial pyrogen are also tolerant to pyrogens from other bacterial species (9). It has been demonstrated in rabbits, however, that tissue pyrogens produce comparable fever in tolerant and non-tolerant animals (2). Similar findings were obtained in three normal dogs whose average fever index when injected with exudate for the first time was 168, and who responded with fevers averaging 161 after they had been made tolerant to the *A. fecalis* vaccine (Fig. 4).

D. *Failure of Thorotrast to Affect the Fever Produced by Peritoneal Exudates.* Tolerance to bacterial endotoxins in rabbits may be reversed within 24 hours by the intravenous administration of 5–10 ml. of Thorotrast (11). The same phenomenon can be observed in dogs, although the doses of Thorotrast re-

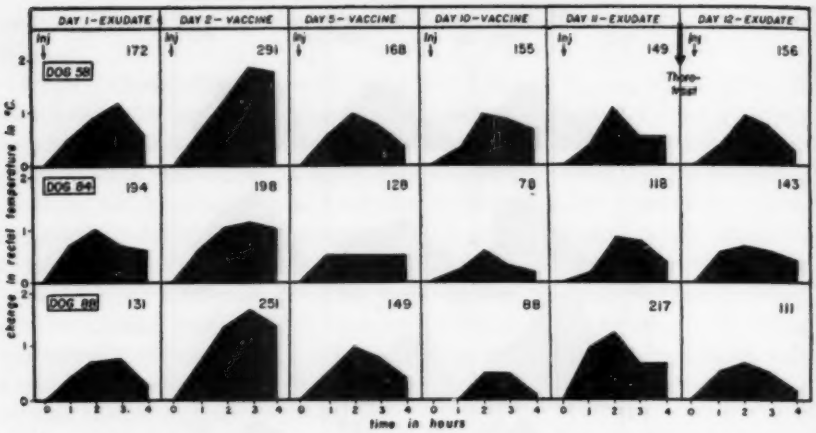

FIG. 4. Temperature curves of 3 dogs, demonstrating that tolerance to *A. fecalis* vaccine does not influence the febrile response to sterile exudates, and that administration of Thorotrast also has no effect on the fever produced by these fluids. Numbers indicate fever indices.

quired to reverse tolerance in these animals are very much greater than in the rabbit (12). Moreover, in normal animals administration of Thorotrast 24 hours prior to injection of bacterial endotoxin augments the febrile response to the toxin. In rabbits, the administration of Thorotrast fails to influence the production of fever by peritoneal exudates (12). Similar results were observed in 3 dogs given 20 ml. of Thorotrast (Fig. 4) before injection of exudates.

These experiments indicate that pyrogenic properties of canine exudates closely resemble those of similar fluids isolated from rabbits, and that these materials from both species differ in several respects from bacterial endotoxins.

DISCUSSION

The finding that sterile canine peritoneal exudates will produce fever when injected intravenously into normal dogs agrees with previous studies in rabbits. The properties of the fluids from both species are similar in that they are heat-labile, produce relatively brief, monophasic fevers, are incapable of inducing tolerance when injected repeatedly and are fully active in animals with well-established tolerance to bacterial endotoxins. The failure of some canine exudates to produce fever may be attributed to the relative mildness of the inflammatory reactions elicited in the peritoneal cavity of dogs, as well as the fact that the test dosage may have been too small in these instances. Furthermore, in previous studies with rabbits, it has not been unusual to find occasional exudates that were non-pyrogenic in the amounts tested.

The finding that canine exudates did not produce fever in the rabbit and

that peritoneal fluids from the latter animals were non-pyrogenic for dogs is of considerable interest. It is improbable that rabbit exudates tested in volumes of 50 to 100 ml. contained insufficient quantities of fever-producing material to elicit a response in dogs. The fact that several of the canine exudates failed to produce fever in rabbits when injected in amounts that were pyrogenic for dogs, makes the factor of dosage an inadequate explanation for the observed results. The possibility that thermogenic factors isolated from tissues, "endogenous pyrogens," may be species-specific in contrast to "exogenous" bacterial endotoxins is intriguing and deserves further study. The repeated failure to produce fevers in rabbits with human exudates and with suspensions of human leukocytes as well as extracts of many other tissues (2, 13) may well be explainable upon this basis. At any rate, the importance of using homologous animals for tests of tissue pyrogens is suggested. Certainly a note of caution in drawing conclusions about the mechanisms of fever in human disease from studies in lower animals is in order.

The nature of the fever-promoting factor or factors in sterile exudates containing leukocytes is not known and as yet these substances have not lent themselves to precise characterization. Numerous attempts in this laboratory to fractionate the thermogenic components of these fluids by zone electrophoresis using starch or polystyrene as a supporting medium have been unsuccessful (14). The system becomes contaminated by bacterial pyrogens so frequently that no consistent patterns have been found. The problem of contamination by these ubiquitous substances remains a serious one because the only method now available for detection of pyrogenic activity is the injection of fractions into animals.

SUMMARY

Sterile canine peritoneal exudates, containing leukocytes, are capable of producing fever when injected intravenously into normal dogs, but are non-pyrogenic in rabbits. The capacity of these fluids to produce fever is destroyed by heating at 90°C. and they do not produce tolerance when injected repeatedly. They are as potent in normal dogs as in dogs with acquired resistance to bacterial endotoxin. Rabbit exudates are non-pyrogenic for dogs. Although these studies add to the evidence that endogenous fever-producing substances may play an important role in the fever of disease, they also point to the possibility of a species-specificity in the activity of such substances that may be extremely important in attempts to interpret the fever of human disease in terms of experimental studies in animals.

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A STUDY OF END-PLATE POTENTIALS

II. Observations on the Actions of Certain Oximes

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Several observers have reported that the inactivation of cholinesterase by different organophosphorus compounds is reversible (1, 2, 3, 4, 5). Among the more effective reactivators are several oximes (6). It is questionable at the present time that any such chemicals are sufficiently effective alone to be of value therapeutically as an antidote for poisoning with certain organophosphorus insecticides (7). However, the variations in reactivating capacities of these compounds (6) make such a use by related substances appear a possibility of the future (7, 8).

Although there has been much study of the mechanism of reactivation of acetylcholinesterase (9) less attention has been directed to other additional effects of such reactivating materials (10, 11). Therefore, the purpose of this paper is to present observations of the effects of three oximes on the end-plate potentials recorded from isolated neuromuscular preparations.

MATERIAL AND METHODS

The experimental technique has been described in detail previously (12), and is modeled after that of Kuffler (13). Essentially the preparation consists of a freshly dissected, isolated and curarized iliofibularis muscle with attached nerve from R. pipiens. Stimulating and recording platinum electrodes are applied to nerve and muscle and the entire ensemble can be raised and lowered into various solutions without shifting the recording electrodes on the preparation. Solutions of 2,3-butanedione 2-oxime (DAM), monoisonitrosoacetone (MINA) and pyridine-2-aldoxime methiodide (PAM) were added to a buffered curare-Ringer's solution to obtain the final concentrations stated in the paper. Routinely the neuromuscular preparation was immersed in each test solution for ten minutes, raised into oil for two minutes and stimulated indirectly once per second supramaximally. The temperature ranged from about 25° to 27° Centigrade during the experiments. Single sweeps on an oscilloscope were photographed and submitted to statistical analyses. The following are samples of eighty-seven experiments (forty-eight with DAM, thirty-two with PAM and seven with MINA).

RESULTS

2,3-butanedione 2-oxime (DAM)

In Figure 1 are shown the changes occurring in the end-plate potential (EPP) following exposure to progressively increasing concentrations of DAM (tracings 2, 3, and 4). As the EPP amplitude decreased the time course of the

potential also changed. There was lengthening of the duration of the rising phase as well as marked prolongation of the decay time.

In Graph I the mean amplitudes of the EPP have been plotted against the molar concentrations of DAM. The changes in amplitudes were at least

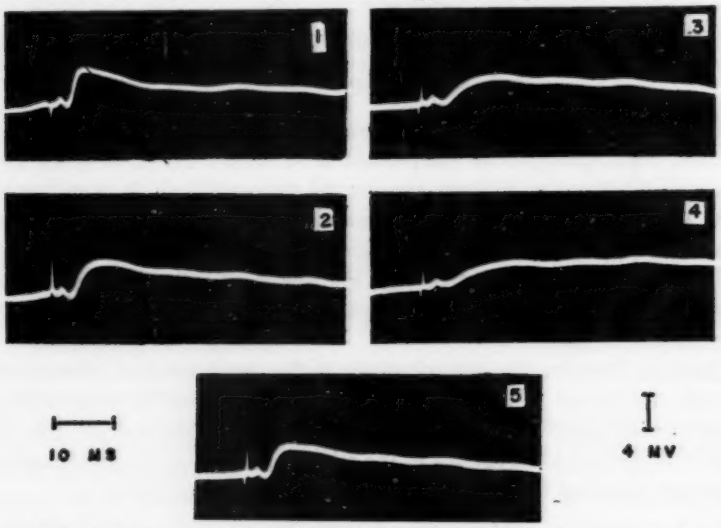
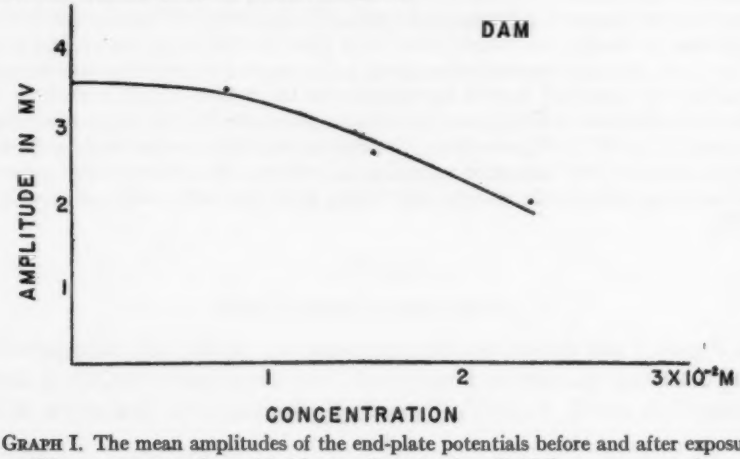
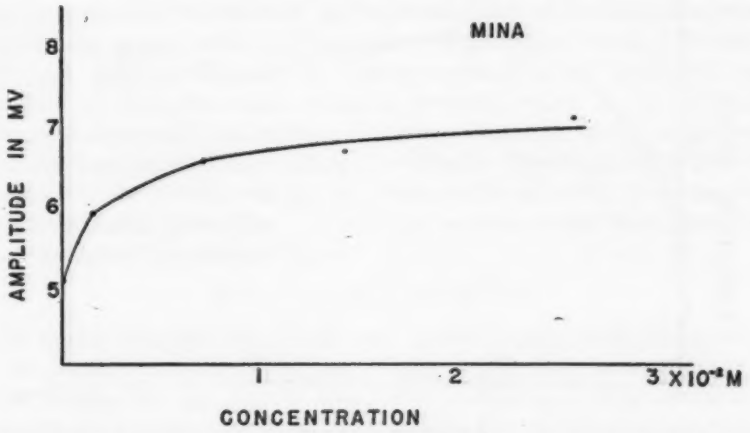


FIG. 1. Tracing 1 represents a control end-plate potential. Tracings 2 through 4 are of the end-plate potentials following 10 minutes exposure to the following concentrations of 2,3-butanedione 2-oxime (DAM): (2) 7.95×10^{-3}M; (3) 1.57×10^{-2}M; (4) 2.34×10^{-2}M. Tracing 5 was made after washing the preparation in control Ringer's solution following the exposure for 10 minutes to 2.34×10^{-2}M concentration of the oxime. The markings represent 10 milliseconds (MS) and 4 millivolts (MV).



GRAPH I. The mean amplitudes of the end-plate potentials before and after exposure to three different concentrations of 2,3-butanedione 2-oxime (DAM) are represented.



GRAPH II. The mean amplitudes of the end-plate potentials before and after exposure to four different concentrations of monoisonitrosoacetone (MINA) are shown.

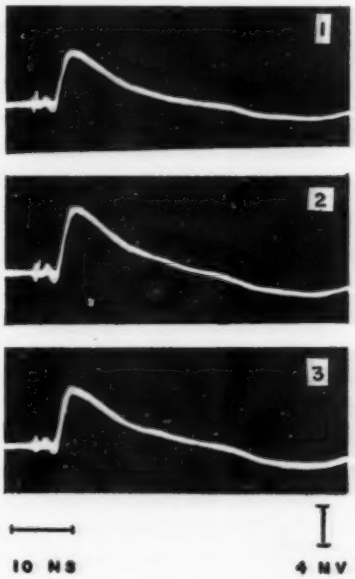
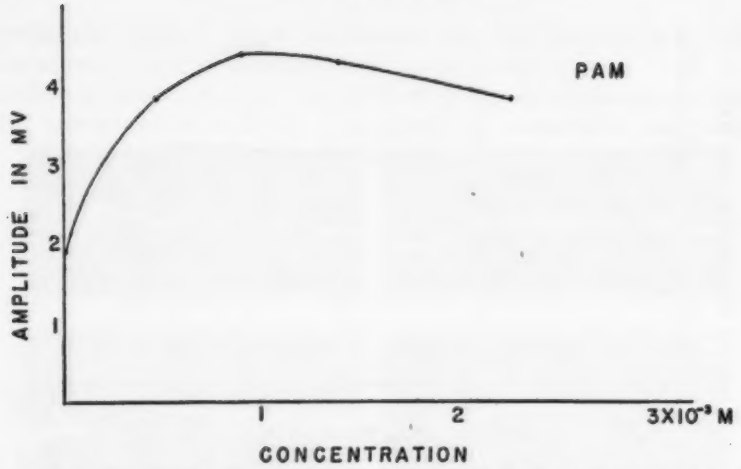


FIG. 2. Tracing 1 represents a control end-plate potential. Tracing 2 shows an increase in amplitude following 10 minutes exposure to 1.6×10^{-3}M concentration of monoisonitrosoacetone (MINA). Tracing 3 represents the return toward normal of the end-plate potential after washing in the control Ringer's solution.



GRAPH III. The mean amplitudes of the end-plate potentials before and after exposure to four different concentrations of pyridine-2-aldoxime methiodide (PAM) are shown.

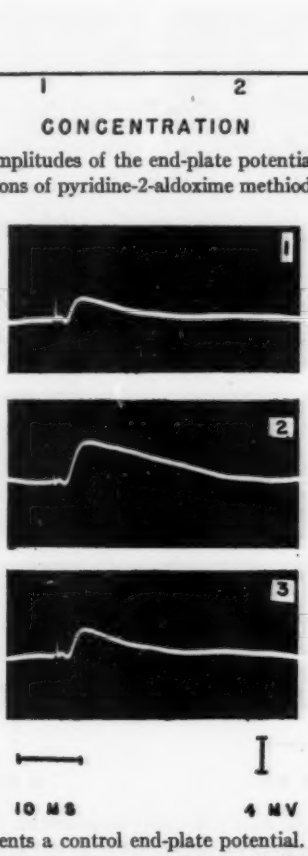


FIG. 3. Tracing 1 represents a control end-plate potential. Tracing 2 shows an increase in amplitude following 10 minutes exposure to 3.14×10^{-4}M concentration of pyridine-2-aldoxime methiodide (PAM). Tracing 3 represents the return toward normal of the end-plate potential after washing in the control Ringer's solution.

partially reversible. For example, the mean amplitude of the end-plate potentials with one control series of stimuli was 4.02 millivolts (standard deviation ±.02)[1] and although following ten minutes exposure to 1.57×10^{-3} M concentration of DAM the mean amplitude dropped to 2.65 ± .33 millivolts; subsequent immersion and washing in a control solution for ten minutes restored the mean amplitude to 3.52 ± .21 millivolts. There was, in other words, a recovery to eighty-seven per cent of normal. Such restoration was associated also with a change in the time course of the potential toward normal, as illustrated by the fifth tracing of Figure 1.

Monoisonitrosoacetone (MINA)

The results obtained with MINA were quite different. As shown in Graph II, the amplitudes of the EPP were increased with rising concentrations of MINA. There does not seem to be a linear relationship between the change in amplitude and the amount of oxime within this particular range. Alterations in the time course were not as striking or as consistent as with DAM. Inability to demonstrate such changes, however, may be due to technical limitations.

Again the oxime effect was reversible as shown in Figure 2. Thus, one control series of observations showed a mean amplitude of the EPP to be 5.04 ± .002 millivolts and, although following exposure to a 1.6×10^{-3} M concentration for ten minutes the mean amplitude rose to 5.9 ± .01 millivolts; subsequent washing in a control solution restored the amplitude toward normal with a mean of 5.25 ± .39 millivolts.

Pyridine-2-aldoxime methiodide (PAM)

Another aspect of an oxime effect is illustrated with rising concentrations of PAM. As shown in Graph III such increases enhanced and subsequently depressed the EPP amplitude. The time course changes of the curves were less impressive than those associated with exposure to DAM. However, as illustrated by the second tracing in Figure 3, there was some prolongation of the time occupied by the ascendng phase and the decay curve of the potential.

These effects were at least partially reversible, as shown by the following. A control series of end-plate potentials had a mean amplitude of 2.62 ± .31 millivolts. Following exposure for ten minutes to 3.14×10^{-4} M concentration of PAM, the mean amplitude rose to 3.81 ± .47 millivolts. Subsequent washing in the control Ringer's solution restored the mean EPP to 2.91 ± .41 millivolts.

DISCUSSION

As demonstrated in the above experiments these oximes had marked effects on the end-plate potential, even in the absence of any previous inactivation

[1] All end-plate potential amplitude measurements will be expressed in millivolts and as the mean ± standard deviation.

of acetylcholinesterase. The alterations observed after exposure to the three compounds were not identical. DAM had a predominantly depressing effect on the height of the peak. The time course of the depolarization and the repolarization of the membrane in the presence of high concentrations of DAM was altered; there was increased duration of both the ascending and the descending phases of the potential. Two possible explanations are: (1) the amount of the transmitter substance active at the end-plate could have been altered; (2) the time constant of the muscle membrane may have been changed. In other words there could have been an alteration in resistance across the membrane, i.e., a change in mobility of ions across the membrane.

In contrast to DAM the compounds MINA and PAM increased the EPP peak markedly. However, in higher concentrations PAM demonstrated a relative depressing effect from the maximum amplitudes obtained with exposure to lower concentrations. Unless acetylcholine output is increased by PAM and MINA, (and there is no evidence for such at the present time) two possible explanations suggest themselves for the initial augmentation of the amplitude of the end-plate potential. First, the acetylcholinesterase function might be so altered that the duration of the transmitter action would be prolonged. Or, secondly, the membrane time constant could be changed. The relative depressive effect with higher concentrations of PAM could be compatible with either explanation. There is evidence that PAM can depress acetylcholinesterase activity (10). Such inhibition could explain the increased EPP peak exemplified by the second tracing in Figure 3. Furthermore, preliminary observations indicate that 3×10^{-3} M concentrations of PAM increase the diffusion of potassium from fresh dog muscle into a surrounding medium of Krebs-Ringer's phosphate solution at 10°C. (14).

Holmes and Robins (10) have tested the direct effect of a variety of oximes on the muscle fibers in a rat phrenic nerve-diaphragm preparation. Using diisonitrosoacetone in 10^{-2} M concentrations as well as triisonitrosopropane in 10^{-3} M amounts they found after two to three hour exposures marked diminution and abolition of response to single stimuli. However, in monoisonitrosoacetone of 10^{-2} M concentrations, a similar preparation after four hours showed only slight decrease in response to single stimuli. These toxic effects were not reversed by washing. The periods of exposure in the present experiments were much shorter and, under the circumstances described, all of the effects of these three oximes were at least partially reversible. The same authors (10) demonstrated a slowing of the conduction velocity in rat gracilis muscle by monoisonitrosoacetone. Presumably differences in experimental techniques account for the fact they observed no effect by oximes on the block with d-tubocurarine.

CONCLUSIONS

The present observations have demonstrated effects of three oximes on the end-plate potential (EPP) of isolated nerve-muscle preparations. The changes described were at least partially reversible. Possible interpretations are mentioned on a preliminary basis.

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ABSTRACTS OF PAPERS PRESENTED BEFORE THE MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY

March 11, 1957

THE BIOSYNTHESIS OF FATTY ACIDS BY MAMMALIAN LIVER

ROBERT G. LANGDON

During the past several years the oxidation of fatty acids by mammalian tissues has been intensively studied in a number of laboratories. It has been found that fatty acid oxidation is carried out exclusively within the mitochondria (1), and the enzymes catalyzing each step in this process have been isolated and purified (2, 3). However, although it is well known that mammalian tissues are capable of synthesizing fatty acids from non-lipid precursors of acetyl-coenzyme A, the details of this synthetic process remained obscure. Recent work in our laboratory (4, 5) has revealed that fatty acid synthesis is catalyzed by enzymes present in the soluble cytoplasm of the liver cell, and that the particulate elements of the cell are without activity in this process. The enzymatic steps leading to the conversion of acetyl CoA to higher fatty acids have been investigated in rat liver and it now appears probable that the following sequence of reactions represents the metabolic pathway followed in fatty acid synthesis:

(1) 2 Acetyl CoA $\rightleftharpoons$ Acetoacetyl CoA + CoA
(2) Acetoacetyl CoA + DPNH + $H^+ \rightleftharpoons$ β-hydroxybutyryl CoA + DPN^+
(3) β-hydroxybutyryl CoA $\rightleftharpoons$ Crotonyl CoA + H_2O
(4) Crotonyl CoA + TPNH + $H^+ \rightleftharpoons$ Butyryl CoA + TPN^+

Repetition of this sequence of reactions presumably leads to the elaboration of the long chain fatty acids characteristically synthesized by mammalian tissues.

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This work was supported in part by the U. S. Public Health Service and was done during the tenure of a Lederle Medical Faculty Award.

EXPERIMENTAL HORMONAL THERAPY OF ATHEROSCLEROSIS: PRELIMINARY OBSERVATION ON THE EFFECTS OF TWO NEW COMPOUNDS

F. W. DAVIS, W. R. SCARBOROUGH, B. M. BAKER, M. L. SINGEWALD AND R. E. MASON

Preliminary observations of the effects of two new compounds in patients with coronary atherosclerosis are reported. The premise that the young female pattern of serum lipo-protein distribution is desirable was tentatively accepted, and efforts to attain this pattern without undue feminization were made. Such effects were accomplished in 50 per cent of

patients treated with one of the two compounds (Manvene). Other evidences of objective improvement were not definitely established, although some suggestion of electrocardiographic and ballistocardiographic improvement over and above that expected in untreated patients was noted. From these relatively short term observations it would seem that the possibility of extended therapy with Manvene, in quantity sufficient to favorably influence serum lipids (and possibly, other objective measurements) exists, with prohibitive feminization occurring in far fewer patients than appears during ordinary estrogen treatment. It should be strongly emphasized that this form of treatment is experimental, and should not be indiscriminantly applied in the care of patients with coronary atherosclerosis until more definitive *human* evidence is available.

AERIAL DISSEMINATION OF PULMONARY TUBERCULOSIS[1]

R. L. Riley, W. F. Wells, C. C. Mills, W. Nyka, P. B. Storey and R. L. McLean

For the past 3 years studies related to the aerial dissemination of pulmonary tuberculosis have been proceeding at the Loch Raven Veterans Administration Hospital. Previous studies by W. F. Wells and others leave no doubt that aerial dissemination of pulmonary tuberculosis occurs experimentally. There has been no convincing demonstration, however, that aerial dissemination is the chief mechanism by which human pulmonary tuberculosis is spread under "normal" conditions.

The experiment to be discussed was designed to test the hypothesis that human pulmonary tuberculosis is spread primarily by airborne droplet nuclei. To test this hypothesis, the rate at which tuberculin negative student nurses become infected (i.e. convert) when exposed to tuberculosis will be compared with the rate at which guinea pigs become infected from breathing the air of a tuberculosis ward.

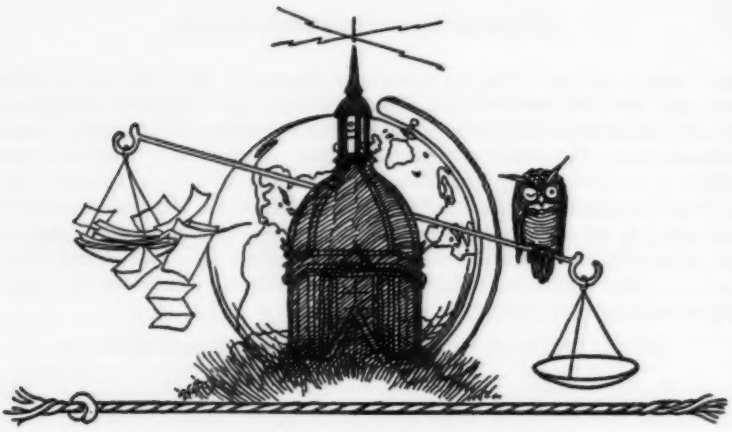
An average figure for the time required for conversion of the tuberculin test in nurses caring for tuberculous patients is 6 months. By selecting the patients and controlling the ventilation of the experimental ward at the Veterans Hospital, we have attempted to make the air of this ward approximate in infectiousness that of hospitals in which nurses are known to convert their tuberculin tests in about 6 months.

Calculations indicate that a student nurse is actually exposed to tuberculosis for about 800 hours before becoming infected. During this time she breathes approximately 16,000 cubic feet of ward air. If it is assumed that the same volume of air must be breathed by guinea pigs before a single quantum of contagium is inhaled, then, to infect 3 guinea pigs per month, the guinea pigs must breathe $3 \times 16{,}000$ or 48,000 cubic feet per month. Since 1 guinea pig breathes only about 240 cubic feet per month, this would require $48{,}000/240$ or 200 guinea pigs. On theoretical grounds, therefore, the necessary conditions for infecting 3 guinea pigs per month by exposure to ward air are: 1) that the patients be infectious; 2) that ward ventilation be controlled at a rate of 30–40 cubic feet per minute per patient; and 3) that approximately 200 guinea pigs be exposed continuously. In fact, the 6 patients on the experimental ward for the 4 months' period from October 1956 through January 1957 varied widely in infectiousness; the ward ventilation was stable at about 37 cubic feet per minute per patient; and an average of about 100 guinea pigs was exposed continuously.

Twelve guinea pigs became infected during the 4 months' period, the monthly rates being 2, 3, 1 and 6. The average rate was 3 infections per month.

The results to date thus show a satisfactory correspondence between theory and practice. By guinea pig infection, enough infective nuclei have been demonstrated in the air to account for the known spread of human tuberculosis in hospitals. This evidence is presented in support of the hypothesis that human pulmonary tuberculosis is spread primarily by airborne droplet nuclei.

[1] Supported by the Veterans Administration and the Maryland Tuberculosis Association.



BOOK REVIEWS

Current Therapy 1957. Latest Approved Methods of Treatment for the Practicing Physician. Edited by HOWARD F. CONN. 731 pp., $11.00. W. B. Saunders Co., Philadelphia, Pa.

This is the ninth in a series of annual revisions of this book under the editorship of Dr. Conn. Again he has been aided by a large group of very able contributors, each in a position to be thoroughly familiar with the therapeutic advances in the field on which he is writing. In those fields where no important therapeutic advance has been made, optimum treatment regimens are outlined with the same clarity and adequate coverage as in the fields of rapid change. Where there is room for difference of opinion, two or more authors are represented. No attempt is made to touch on diagnostic methods or disease processes.

This series is a valuable contribution to medical literature. For the medical historian it records the thinking of the current authorities. For the medical student or house officer short of experience and familiarity with the treatment of disorders in widely diverse special areas it collects reliable information in a single volume. This applies also to the practitioner needing reassurance that his regimen for a given disease is the proper one, and for the subspecialist who needs no help in his own bailiwick, but finds himself a bit behind in others.

Dr. Conn is to be congratulated for his vision in seeing the need for this series, and his industry in continuing it at its present high level.

ROBERT E. MASON

Liver: Structure and Function. By HANS POPPER AND FENTON SCHAFFNER. 777 pp., $20.00. McGraw-Hill Book Co., New York, N. Y.

The seminal influence of Hans Popper upon students of all phases of hepatic structure, function, and pathophysiology has been widely recognized for the past seven or eight years. The variety and intensity of his interests have resulted in important articles appearing in so many diverse journals of basic science and clinical medicine that the true unity of his thinking has been somewhat obscured. It is a pleasure now to see all these different facets of his work brought together into one handsomely published volume, where the extraordinary efforts he has made to unify and redefine concepts of hepatic physiology and pathology can be studied and digested at leisure. With the assistance of Dr. Schaffner,

the book has been designed to be a complete reference work on all phases of liver disease, and so it is, but its unique value lies in its critical and intrepid reevaluation of our ideas about hepatic structure and function as altered by injury. From the comprehensive bibliography one may quickly see the international perspective commanded by the group which gathered around Dr. Popper in Chicago; the brilliant way in which the authors use this bibliography is a tribute to their integrity and thoroughness, as well as to the way in which they have seen their subject "whole" from the beginning to end. An addendum to each section brings the bibliography up to date of going to press.

This reviewer was particularly impressed by the approach to normal structure and function, to which 178 pages of lucid writing and pertinent illustrative material, much of it entirely new, are devoted. The second section, "Pathologic Phenomena in the Hepatobiliary System" follows naturally along the lines so clearly described in Part I, and is remarkable for the careful definition of terms used rather loosely in the general medical literature. As would be expected, the chapters on the structural and functional changes in cirrhosis are particularly valuable. Part III, "Clinical Study of Hepatic Function and Structure" includes the methods of carrying out the procedures employed to test hepatic function as well as their interpretation, and in general is quite satisfactory. It is a little surprising that only 6 pages are devoted to liver biopsy as such, although of course biopsy material is generously used as the basis for many of the statements made elsewhere in the book. Diffuse diseases of the liver are treated *in extenso* in Part IV; the section on chronic viral hepatitis is a valuable contribution, as is the critical analysis of nutritional injury, where studies carried out on animal and man are kept carefully separated. Chapter 52 summarizes the recent reclassification of cirrhosis published by Dr. Popper in 1955. Part V is devoted to focal diseases of the liver, including diseases of the blood vessels, Part VI to tumors of the liver and biliary tree, and Part VII to "Internal and External Environment and the Liver", in which a large mass of material as yet poorly understood is brought together and dealt with in an earnest, if not completely satisfactory manner.

This large and beautifully illustrated book is by any standards a remarkable achievement, but its true value is best appreciated by those who do not underestimate the complexity of liver diseases, are familiar with past efforts to deal with hepatic structure in health and disease, and are willing to meet the authors halfway in their serious efforts to redefine, reevaluate, and reconstruct properly documented analyses of this subject. Since the approach is basically that of the experimental pathologist and the clinical pathophysiologist, the casual physician looking for a compact easy-to-read discussion of liver disease will not find this book his cup of mild tea. It is a strong brew, deliberately concocted for the reader who is prepared to stay for a prolonged but enjoyable feast.

ALBERT I. MENDELOFF

Medical Effects of the Atomic Bomb in Japan. National Nuclear Energy Series. Manhattan Project Technical Section. Division VIII. Volume 8. Edited by ASHLEY W. OUGHTERSON AND SHIELDS WARREN. 477 pp., $8.00. McGraw-Hill Book Co., New York, N. Y.

This is in effect a progress report on the results of the Hiroshima and Nagasaki bombs of 1945. There is little added by way of new information on the biological effects of radiation; a full assessment of these effects will obviously require many more years. The major contribution made is the unemotional recital of the causes of death, the clinical picture seen preceding death in the fatally injured, and the hematological and pathological changes observed in all types of injury associated with the explosions. Considerable emphasis is placed on the disruption of normal medical facilities as the result of the destructive effects of the explosion. The causes of death and of injury were heat, ionizing radiation and blast in de-

creasing order of importance. A major conclusion of this report is: "If the mortality from atomic-bomb explosions is to be effectively reduced, chief reliance must be placed on preventive measures".

This volume has other than strictly medical and pathological importance. It is hoped that it will be as widely read and appreciated as it deserves to be.

FRANCIS P. CHINARD

New Bases of Electrocardiography. By DEMETRIO SODI-PALLARES with the collaboration of ROYALL M. CALDER. 727 pp., $18.50. The C. V. Mosby Co., St. Louis, Missouri.

This work, the English translation of the Third Spanish edition, presents a most comprehensive effort to relate the principles of electricity and electrophysiology to the interpretation of the electrocardiogram. The entire first chapter and a great number of subsequent passages endeavour to orient these principles in terms of simple mathematical analyses. However, simplicity is not always preserved and thereby some of the book's value as a basic text is lost. As an advanced text and reference source there is much to be recommended.

Many of the chapters, although related, form excellent monographs in themselves and can be read independently. Particularly well done are the sections on "The Einthoven Triangle", "The Activation Process of the Human Heart", "The Ventricular Gradient", and "The Intracavitary Potential'. For those physicians who are undeterred by the use of solid angles, differential equations and integrals a long appendix provides a thorough review of first principles ranging from Gauss and Helmholtz to the membrane physiology of Cole and Curtis. Many of these appendiceal interpretations are those of Frank Wilson and constitute an impressive memorial to him. Such interpretations, extended mathematically and experimentally by Sodi-Pallares, form the "new bases" of the book. The helpfulness of the appendix would be much increased by a table of contents and increased usage of exact page references to the appendix.

The work contains many illustrations the bulk of which refer to the clinical problems involved in the interpretations of the ventricular complex.

S. H. BOYER

BOOKS RECEIVED FOR REVIEW

The Care of the Expectant Mother. By JOSEPHINE BARNES. 270 pp., $7.50. Philosophical Library, New York, N. Y.

Change and Dilemma in the Nursing Profession. By LEONARD REISSMAN AND JOHN H. ROHRER. 450 pp., $6.80. G. P. Putnam's Sons, New York, N. Y.

Clinical Cardiopulmonary Physiology. Sponsored by the American College of Chest Physicians. Edited by BURGESS L. GORDON. 759 pp., $15.75. Grune & Stratton, Inc., New York, N. Y.

Clinical Physiology. The Functional Pathology of Disease. Edited by ARTHUR GROLLMAN. 854 pp., $12.50. McGraw-Hill Book Co. Inc., New York, N. Y.

Digestive System, Part III, Volume 3, Liver, Biliary Tract and Pancreas. Prepared by FRANK H. NETTER. Edited by ERNST OPPENHEIMER. The Ciba Collection of Medical Illustrations. 165 pp., $10.50. Ciba Pharmaceutical Products, Inc., Summit, N. J.

The Doctor as a Witness. By JOHN EVARTS TRACY, 221 pp., $4.25. W. B. Saunders Co., Philadelphia, Pa.

Dorland's Illustrated Medical Dictionary, 23rd edition. 1598 pp., $12.50. W. B. Saunders Co., Philadelphia, Pa.

The Epilepsies. Electro-Clinical Correlations. By HENRI GASTAUT. Translated by MAR.

A. B. BRAZIER. (American Lecture Series). 176 pp., $4.75. Charles C Thomas, Springfield, Ill.

Expectant Motherhood, 3rd edition, revised. By NICHOLSON J. EASTMAN. 198 pp., $1.75. Little, Brown & Co., Boston, Mass.

Fundamentals of Clinical Neurophysiology. By PAUL O. CHATFIELD. 392 pp., $8.50. Charles C Thomas, Springfield, Ill.

History of Nursing Source Book. A Compilation of Selections from Original Documents. By ANNE L. AUSTIN. 480 pp., $7.50. G. P. Putnam's Sons, New York, N. Y.

Hypothalamic-Hypophysial Interrelationships. A Symposium of the Third Annual Scientific Meeting of the Houston Neurological Society, Texas Medical Center, Houston, Texas. Compiled and Edited by WILLIAM S. FIELDS, Roger Guillemin and Charles A. Carton. 156 pp., $4.75. Charles C Thomas, Springfield, Ill.

New and Nonofficial Remedies. Evaluated by the Council on Pharmacy and Chemistry of the American Medical Association for 1957. 582 pp., $3.35. J. B. Lippincott Co., Philadelphia, Pa.

Physiologic Principles of Surgery. Edited by LEO M. ZIMMERMAN AND RACHMIEL LEVINE. 988 pp., $15.00. W. B. Saunders Co., Philadelphia, Pa.

The Principles and Art of Plastic Surgery, Vols. I and II. By SIR HAROLD GILLIES AND D. RALPH WILLARD, JR. 652 pp., $35.00. Little, Brown & Co., Boston, Mass.

Principles of Urology. An Introductory Textbook to the Diseases of the Urogenital Tract. By MEREDITH F. CAMPBELL. 622 pp., $9.50. W. B. Saunders Co., Philadelphia, Pa.

Rheumatic Diseases, Rheumatism and Arthritis. By HEINRICH G. BRUGSCH. 330 pp., $10.00. J. B. Lippincott Co., Philadelphia, Pa.

Steppingstones to Professional Nursing, 2nd edition. By LUELLA J. MORISON. 474 pp., $4.75. The C. V. Mosby Co., St. Louis, Mo.

A Symposium on the Chemical Basis of Heredity. Sponsored by the McCollum-Pratt Institute of The Johns Hopkins University with support from the Atomic Energy Commission. Edited by WILLIAM D. MCELROY AND BENTLEY GLASS. 848 pp., $12.50. The Johns Hopkins Press, Baltimore, Md.

Ultramicro Methods for Clinical Laboratories. By EDWIN M. KNIGHTS, JR., RODERICK P. MACDONALD AND JEAN PLOOMPUU. 128 pp., $4.75. Grune & Stratton, Inc. New York, N. Y.

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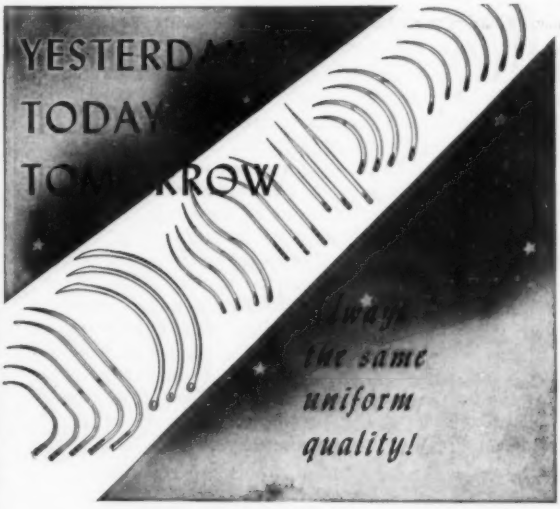

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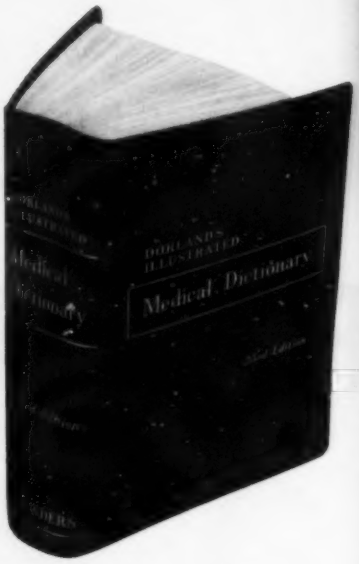

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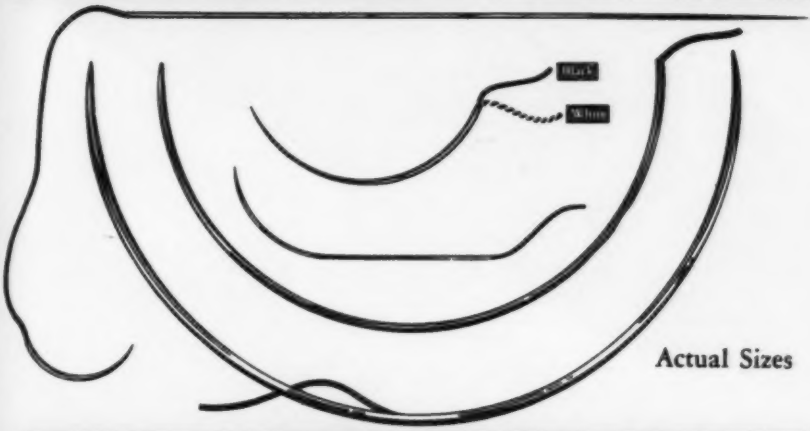

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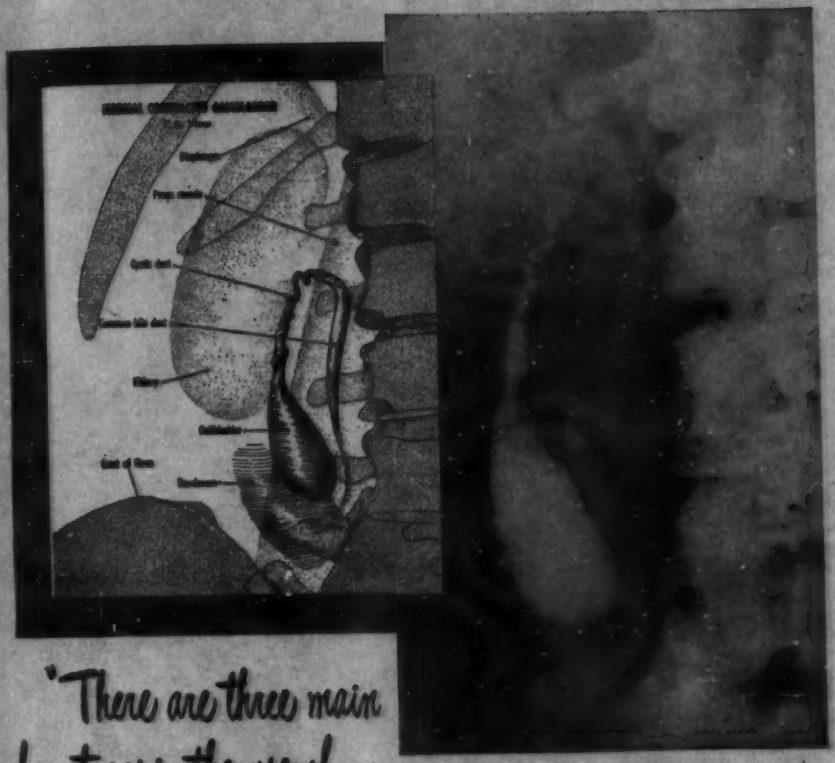

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